Synthesis of Isoaminile Mediated by Enzymes

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Abstract: A lipase-mediated synthesis of all four enantiomers of isoaminile is reported. The key issues of the paper are: (i) enantioselective acetylation of allylic alcohol (*E*)-(±)-**5** to give (*E*,*S*)-**5** (ee = 92%) and (*E*,*R*)-**6** (ee >99%); (ii) Claisen–Johnson rearrangement of *R* and *S* enantiomers of **5** to generate the quaternary benzylic stereocenter; (iii) chromatographic separation of aldehyde diastereoisomers; (iv) X-ray structure of aldehyde (2*R*,4*R*)-**10**; (v) unpredicted formation of lactone **12** during the hydrolysis of **11**.

Key words: drugs, enzymes, enantiomeric resolutions, rearrangements, lactones

Isoaminile **1** (Figure 1) is an antitussive agent, discovered by Hoechst and widely used as therapeutic agent.[1] The molecule contains two stereogenic centres: one centre is a quaternary carbon at the benzylic position and the second at C(4) position bears an amine group. The isoaminile-cyclamate salt is commercialized in racemic form as tablets or syrup under the trade name Peracon®.

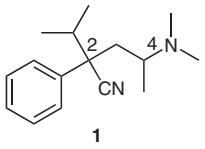

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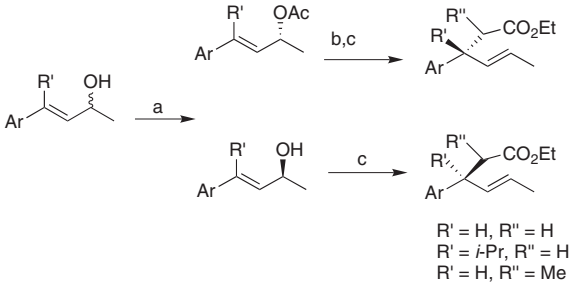
Figure 1

Our interest in this and related compounds relies on the presence of a benzylic stereogenic center. Indeed, during the last years we have been involved in the development of a general synthetic methodology that allows the enantioselective generation of either tertiary or quaternary benzylic carbons. This synthetic route consists of the Claisen rearrangement of optically pure allylic alcohols, which can be easily prepared by enzymatic asymmetric esterification (Scheme 1).[2]

Certainly, the generation of benzyl stereogenic centres remains a chemical delicacy of modern organic synthesis, and so far, most of the strategies that have been reported in the literature are mainly based on transition metal asymmetric catalysts.[3] However, the advantages of using a methodology based on the enzymatic resolution of allylic alcohols are: (i) acetylation occurs always with excellent ee on a large variety of substrates; (ii) enzyme is commercially available and can be reused several times without loss of efficiency; (iii) the reaction does not require any special set up, which is usually a tedious and time consuming operation; (iv) laboratory equipment and the synthetic skills needed are of standard level. Indeed, we have successfully employed this methodology for the preparation of several different targets such as a drug,[2a,b] a natural product,[2d] a solving agent[2c] and a fragrance.[2e]



Scheme 1 Key: (a) Enzymatic resolution of allylic alcohols; (b) hydrolysis of acetyl derivative; (c) Claisen rearrangement to give either the quaternary or the tertiary benzylic stereocenter.

To the best of our knowledge neither enantioselective synthesis nor resolutions of isoaminile have been described. Herein, we report the first preparation of all four stereoisomers of **1** in enantimerically pure form.

The synthesis of the racemic allylic alcohols (*E*)-(±)-**5** and (*Z*)-(±)-**5** is outlined in Scheme 2. Horner–Emmons olefination of ketone **2** with the diethoxylphosphoryl ethylacetate **3**, using NaH as base, gave an almost 1:1 mixture of the configurational isomers (*E*)-**4** and (*Z*)-**4**, in a yield of ca. 80%.[4,5] The two isomers were easily separated by column chromatography and the configuration of the double bond was assigned by analysis of the allylic ^{1}H NMR coupling constant. In fact, on the basis of our experience based on similar compounds, we found out that J = 1.0 Hz is typical for *E* isomers, whereas, the *Z* isomers do not show any coupling constant. In addition, strong NOE between the protons H-C(4) and H-C(3) for the alcohol (*Z*)-**5** and between the protons H-C(5) and H-C(2) of (*E*)-**5** confirmed our initial assignment (Scheme 2).[2b]

The transformation of both *E*- and *Z*- isomers of **4** to the corresponding alcohols, (*E*)-(±)-**5** and (*Z*)-(±)-**5** was accomplished by a three step reaction sequence consisting of: (i) reduction of the ester group with Red-Al; (ii) oxida-

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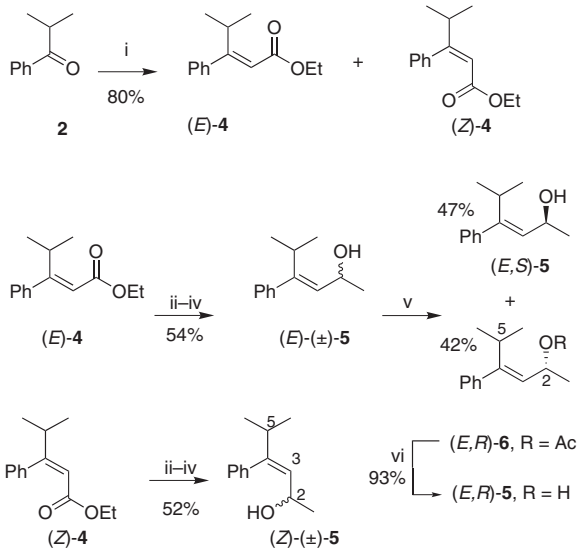
tion of the primary alcohol to the corresponding aldehyde with MnO_2; (iii) addition of MeMgI to the carbonyl group to give the allylic alcohols (*E*)-(±)-**5** and (*Z*)-(±)-**5**, in an overall yield of 54% and 52%, respectively. The enzymatic (lipase PS) acetylation of a solution of (*E*)-(±)-**5** in TBME, using vinyl acetate as acetylating agent, afforded after 9 days the acetate (*E*,*R*)-**6** (99.5% ee, vide infra) and the non-converted alcohol (*E*,*S*)-**5** (92% ee by chiral HPLC), which were easily separated by column chromatography. The absolute configurations were initially assigned by extrapolation from other enzymatic esterifications carried out on similar allylic alcohols. In all previous cases the enzyme acetylated always the *R* enantiomer of the alcohol with high a ee.[2a–e]



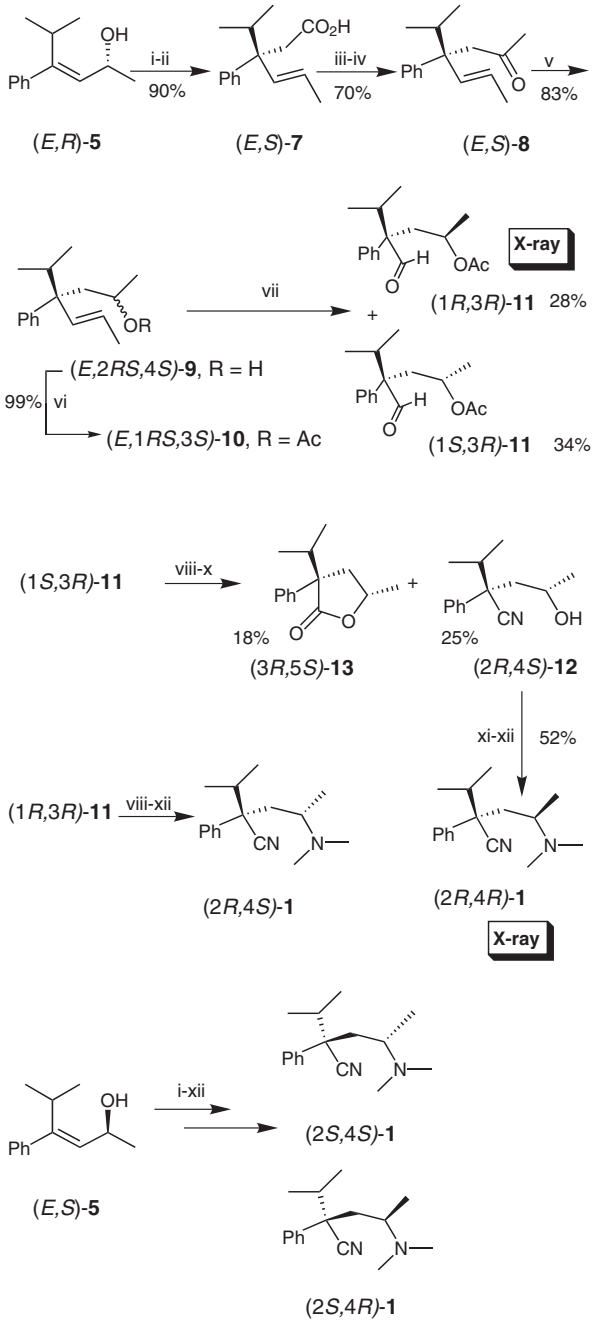
Scheme 2 *Reagents and conditions*: (i) $(OEt)_2POCH_2CO_2Et$ **3**, refluxing toluene; (ii) Red-Al, THF, r.t.; (iii) MnO_2, CH_2Cl_2, r.t. (iv) MeMgI, Et_2O, 0 °C; (v) Lipase PS, vinyl acetate, Et_2O; (vi) KOH, MeOH–H_2O.

The kinetic resolution of (*Z*)-(±)-**5**, carried out under the same experimental conditions used for the resolution of (*E*)-(±)-**5**, was very slow. Since, after 20 days only 28% (by GC) of the alcohol was converted to the acetate, this resolution was abandoned in favor of the first one. The result was consistent with other enzymatic esterfications of similar (*Z*) allyl alcohols.[2b]

The (*E*,*R*)-**5** enantiomer (99.5% ee by chiral HPLC) was obtained by hydrolysis of (*E*,*R*)-**6** with KOH in MeOH in almost quantitative yield.

Thus, Claisen–Johnson rearrangement of alcohol (*E*,*R*)-**5** with triethylorthoacetate (TEOA), in the presence of a catalytic amount of propionic acid, gave the corresponding ethyl ester, which was hydrolyzed affording the acid (*E*,*S*)-**7** in an overall yield of around 90% (Scheme 3). The latter was then transformed to ketone (*E*,*S*)-**8** by a two-reaction sequence: (i) formation of the mixed anhydride and, (ii) addition of MeMgI to give (*E*,*S*)-**8**, in an overall yield of 70%. Reduction of the latter with $NaBH_4$ gave an almost 1:1 mixture of the two diastereomeric alcohols (*E*,2*RS*,4*S*)-**9**. Lipase catalyzed biotransformation of this mixture to the corresponding acetate with vinyl acetate as acyl donor, was very slow. This observation was attributed to the steric hindrance exerted by the bulky adjacent quaternary carbon.

Thus, on the way to reduce such steric hindrance by cutting the double bond with ozonolysis of the acetate derivative (*E*,1*RS*,3*S*)-**10** followed by work-up with PPh_3 to



Scheme 3 *Reagents and conditions*: (i) TEOA, cat. $CH_3CH_2CO_2H$, 150 °C; (ii) KOH, MeOH–H_2O, reflux; (iii) $ClCO_2Et$, Et_3N, CH_2Cl_2, 0 °C; (iv) MeMgI, Et_2O, –20 °C; (v) $NaBH_4$, MeOH, r.t.; (vi) Ac_2O, pyridine, r.t.; (vii) O_3, MeOH–CH_2Cl_2, –78 °C, PPh_3; (viii) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, r.t.; (ix) Ac_2O, NaOAc, reflux; (x) KOH, MeOH–H_2O, r.t.; (xi) TsCl, pyridine, r.t.; (xii) $NHMe_2$, *i*-PrOH, 120 °C.

give the two aldehydes (1*R*,3*R*)-**11** and (1*S*,3*R*)-**11**, we unexpectedly found out that the latter aldehydes were separable by column chromatography. Moreover, the crystalline nature of (1*R*,3*R*)-**11** allowed a simplification of the initial separation procedure: (1*R*,3*R*)-**11** was mainly obtained by simple crystallization in hexane, whereupon the column chromatography of the mother-liquor, enriched of diastereoisomer (1*S*,3*R*)-**11**, was facilitated.

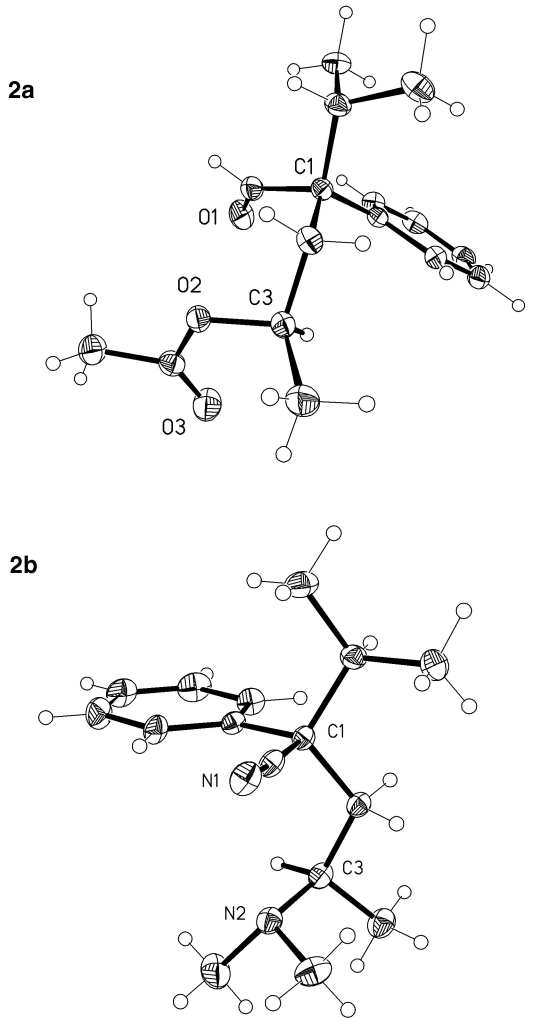


Figure 2 X-ray structure of: (a) aldehyde (1*R*,3*R*)-**11** and (b) amine (2*R*,4*R*)-**1**. The atoms labeling does not corresponds to IUPAC rules.

The X-ray structure analysis of aldehyde (1*R*,3*R*)-**11**, on the basis of Flack parameter[6] (refined by SHELX97),[7] confirmed the absolute configuration of compound (*E*,*R*)-**6** which was initially assigned on the basis of chemical considerations.

The molecular structure shows a cisoidal relation between the carbonyl and the acetate groups (see Figure 2a). In the crystal packing the molecules are placed into sheets parallel to ac plane. No short interactions are observed among the molecules of the same sheet or between adjacent sheets.

The alcohol (2*R*,4*S*)-**12** was obtained by a three steps reaction sequence consisting of: (i) treatment of aldehyde (1*S*,3*R*)-**11** with NH_2OH to give the corresponding oxime derivative; (ii) dehydration of the latter with Ac_2O and NaOAc; followed by (iii) hydrolysis of the ester group with KOH in MeOH at room temperature. The reaction sequence afforded (2*R*,4*S*)-**12** in a modest overall yield of 25%. In fact, the hydrolysis of ester group proceeded always with the formation of lactone (3*R*,5*S*)-**13** and with the incomplete conversion of the ester to the alcohol. Attempts to eliminate or just reduce the formation of this side product, by carrying out the reaction at low temperature and using just one equivalent of KOH, failed.

The hydrolysis of nitriles with KOH in alcoholic solvents occurs often at high temperature. To the knowledge of the authors no other hydrolysis of acetoxy-nitriles with KOH to give lactones has been reported.[8] Moreover, since the hydrolysis of a similar acetoxy-nitrile bearing the acetoxy group at C(5) position, with KOH in refluxing EtOH, gave the corresponding alcohol in an excellent 85% yield,[2b] the five-membered lactone formation is likely to be promoted by the presence of AcO-C(4) which once hydrolyzed to the alcohol favors the following hydrolysis of the nitrile to give the lactone.

Finally, the (2*R*,4*R*)-enantiomer of **1** was obtained by nucleophilic attack of $NH(Me)_2$ (H_2O, 40%) in *i*-PrOH on the tosyl derivative of the alcohol (2*R*,4*S*)-**11** in a good yield (52%). The amine was isolated by a simple acid-base washing extraction. Surprisingly, the amine obtained was a crystalline solid, whereas, the mixture of the two diastereoisomers is described in the patent as a liquid.[1]

The molecular structure of amine (2*R*,4*R*)-**1**, as determined by X-ray diffraction analysis, is shown in Figure 2b. The amino and nitrile groups exhibit a *cis* conformation with respect to C1…C3 direction. In this case, the absolute configuration of the amine could not be confirmed by X-ray analysis on the basis of refinement of Flack parameter, which led to an inconclusive value. However, a significant difference was observed between the final agreement factors, *R*1, of the two opposite configurations (0.065 and 0.076 for the selected configuration and for the inverse one, respectively). In the crystal packing, no short intermolecular interactions are observed. The crystal structure determination data are summarized in Table 1.

The other remaining enantiomers of **1** were obtained with similar yields following the same synthetic protocol shown in Scheme 3.

All solvents and reagents were purchased by the suppliers and used without further purification. *Burkholderia cepacia* lipase (Lipase PS, Amano Pharmaceuticals Co., Japan) was employed in this work. Chiral HPLC analyses were performed on a Chiralcel OD column (Daicel-Japan) installed on a Merck–Hitachi L-6200 apparatus with: flow rate 0.6 mL/min; UV detector (254 nm), and hexane–*i*-PrOH (95:5) as eluent. GC–MS analyses were performed on a HP 6890 gas-chromatograph equipped with a 5973 mass-detector, using a HP-5MS column (30 m × 0.25 mm × 0.25 mm). The follow-

Table 1 Crystal Data of Aldehyde (1*R*,3*R*)-**11** and (2*R*,4*R*)-**1**

Formula	(1*R*,3*R*)-**11** $C_{16}H_{22}O_3$	(2*R*,4*R*)-**1** $C_{16}H_{24}N_2$
Formula weight	262.34	243.36
Crystal dimensions (mm)	0.30 × 0.40 × 0.05	0.50 × 0.65 × 0.02
Crystal system	Orthorhombic	Hexagonal
Space group	$P2_12_12_1$	$P6_5$
Unit cell parameters *a* [Å]	7.282 (1)	9.049 (1)
b [Å]	13.219 (1)	9.049 (1)
c [Å]	15.627 (1)	33.160 (4)
α (°)	90	90
β (°)	90	90
γ (°)	90	120
Volume [Å^3]	1504.3 (3)	2351
Z	4	6
Density (calcd) [g cm^{-3}]	1.158	1.031
Adsorption coefficient μ [mm^{-1}]	0.629	0.459
F(000)	568	798
Diffractometer	Siemens P4	Siemens P4
Radiation, wavelength [Å]	CuKα, 1.54179	CuKα, 1.54179
No. of reflections for cell determination	57	67
θ range for cell determination [°]	6.72–23.25	5.72–33.8
θ range of data collection [°]	4.38–67.91	5.6–65.83
Completeness to 2θ	93.6%	99.9%
hkl limits	$-7 \le h \le 7, -12 \le k \le 15, -18 \le l \le 14$	$-9 \le h \le 9, -10 \le k \le 6, -24 \le l \le 39$
Reflections collected/unique/(R_{int})	2351/2215/(0.025)	4805/1748/(0.128)
No. of observed reflections [I > 2σ (I)]	1957	1488
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2215/0/173	1748/1/168
Goodness of fit on F^2	1.037	1.073
Final *R* indices [I > 2σ(I)]	*R*1 = 0.0423	*R*1 = 0.0653
R indices (all data)	*R*1 = 0.0498	*R*1 = 0.0807
Extinction coefficient	0.012 (1)	0.019 (2)
Largest difference peaks and hole [e·Å^{-3}]	0.145 and –0.113	0.189 and –0.210
Flack X parameter	0.01 (3)	–

ing temperature program was employed: 60 °C (1 min)–6 °C/min–150 °C (1 min)–12 °C/min–280 °C (5 min). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on a Bruker DMX spectrometer (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz). The chemical shift scale is based on internal TMS. *J* values are given in Hz. Optical rotations were measured on a Dr. Kernchen Propol digital automatic polarimeter. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates.

(*E*)-4-Methyl-3-phenyl-2-ethylpentenoate [(*E*)-4)] and (*Z*)-4-Methyl-3-phenyl-2-ethylpentenoate [(*Z*)-4)]

To an ice-cooled solution of NaH (48.0 g, 1.2 mol, 60% oil dispersed) in toluene (0.5 L) was added dropwise a solution of diethoxylphosphoryl ethylacetate **3** (269 g, 0.8 mol) in toluene (0.2 L) under a N_2 atmosphere. To this solution was added dropwise after 1 h a solution of ketone **2** (118 g, 0.8 mol) in toluene (0.2 L). After 14 h at refluxing temperature the reaction mixture was quenched with water (0.5 L), extracted with Et_2O (3 × 0.3 L), dried over Na_2SO_4 and the solvent was removed under reduced pressure affording a yellow oil. Column chromatography of the crude material [SiO_2, hexane–EtOAc (9:1)] gave the isomers of **4** in the following order.

(*E*)-4

Yield: 72.3 g (41.5%); oil.

^{1}H NMR: δ = 725–7.12 (m, 5 H, ArH), 5.70 (s, 1 H, CH=), 4.21 (q, *J* = 7.2 Hz, 2 H, CH_2), 4.11 (septuplet, *J* = 7.0 Hz, 1 H, CH), 1.30 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.07 [d, *J* = 7.2 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR: δ = 167.2 166.4, 141.1, 128.0, 127.9, 127.8, 118.9, 60.0, 29.9, 21.6, 14.5.

GC–MS (t_R= 18.47 min): *m*/*z* = 218 (100) [M$^+$], 189 (5), 172 (10).

Anal. Calcd for $C_{14}H_{18}O_2$ (218.3): C, 77.03; H, 8.31. Found: C, 77.14; H, 8.90.

(*Z*)-4

Yield: 68.3 g (39.2%); oil.

^{1}H NMR: δ = 7.44–7.21 (m, 3 H, ArH), 7.15–7.05 (m, 2 H, ArH), 5.89 (d, *J* = 1.0 Hz, 1 H, CH=), 4.00 (q, *J* = 7.1 Hz, 2 H, CH_2), 4.11 (dseptuplet, *J* = 6.9, 1.0 Hz, 1 H, CH), 1.11 [d, *J* = 7.0 Hz, 6 H, $CH(CH_3)_2$], 1.05 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR: δ = 166.4, 165.0, 140.3, 127.7 127.3, 127.2, 115.9, 59.7, 37.2, 21.2, 13.9.

GC–MS (t_R = 17.48 min): *m*/*z* = 218 (100) [M$^+$], 189 (10), 172 (10).

Anal. Calcd for $C_{14}H_{18}O_2$ (218.3): C, 77.03; H, 8.31. Found: C, 77.17; H, 8.93.

(*E*)-5-Methyl-4-phenyl-3-hexen-2-ol [(*E*)-(±)-5]

To an ice-cooled solution of (*E*)-**4** (63.2 g, 0.29 mol) in THF (0.5 L) was added dropwise Red-Al (91.1 mL, 3.5 M in toluene) under a N_2 atmosphere. After that the reaction mixture was allowed to reach the r.t., after which the reaction mixture was poured into ice (200 mL), neutralized with HCl (0.1 N), and washed with Et_2O (3 × 0.3 L). The combined organic layers were washed with sat. $NaHCO_3$ (0.3 L) and sat. brine (0.3 L) and then dried over Na_2SO_4. The solvent was removed under reduced pressure yielding the primary alcohol as a yellow oil of sufficient purity for the next step. To a solution of the alcohol in CH_2Cl_2 (0.8 L) was added MnO_2 (60 g). After 24 h the suspension was filtered on a pad of celite. The solvent was removed under reduced pressure to give the aldehyde as a yellow oil, which was used without purification in the next step. To an ice-cooled solution of MeMgI in Et_2O (500 mL) freshly prepared in the usual way (Mg: 8.4 g, 0.35 mol, and MeI: 21.3 mL, 0.35 mol), was added a solution of the aldehyde in Et_2O (100 mL). After 2 h the reaction mixture was poured into ice (100 mL) and sat. NH_4Cl (100 mL), washed with Et_2O (2 × 0.3 L), and dried over Na_2SO_4. The solvent was removed under reduced pressure affording an oil. Column chromatography of the crude material [SiO_2, hexane–EtOAc, (8:2)] gave alcohol (*E*)-(±)-**5**; yield: 27.6 g (54%); pale yellow oil.

^{1}H NMR: δ = 7.32–7.12 (m, 5 H, ArH), 5.31 (d, *J* = 8.3 Hz, 1 H, CH=), 4.83 (dq, *J* = 8.4, 6.1 Hz, 1 H, C*H*OH), 3.10 [septuplet, *J* = 7.0 Hz, 1 H, C*H*$(CH_3)_2$], 1.55 (br s, 1 H, OH), 1.34 (d, *J* = 6.1 Hz, 3 H, HOCHC*H*$_3$), 1.11–1.01 [m, 6 H, CH(C*H*$_3$)$_2$].

^{13}C NMR: δ = 149.1, 142.8, 133.4, 129.2 128.2, 127.2, 64.7, 30.5, 24.7, 22.9, 22.7.

GC–MS (t_R = 16.34 min): *m*/*z* = 190 (2) [M$^+$], 172 (5), 157 (20).

Anal. Calcd for $C_{13}H_{18}O$ (190.3): C, 82.06; H, 9.53. Found: C, 82.14; H, 9.47.

(*Z*)-5-Methyl-4-phenyl-3-hexen-2-ol [(*Z*)-(±)-5]

The alcohol (*Z*)-(±)-**5** was obtained following the same procedure as used for the synthesis of (*E*)-(±)-**5** starting from the ester (*Z*)-**4** (61.0 g, 0.28); yield: 27.2 g (52%); yellow oil.

^{1}H NMR: δ = 7.43–7.08 (m, 5 H, ArH), 5.31 (dd, *J* = 0.8, 8.3 Hz, 1 H, CH=), 4.11 (dq, *J* = 8.2, 7.0 Hz, 1 H, C*H*OH), 2.53 [dseptuplet, *J* = 0.8, 7.0 Hz, 1 H, C*H*$(CH_3)_2$], 1.55 (br s, 1 H, OH), 1.34 (d, *J* = 6.0 Hz, 3 H, HOCHC*H*$_3$), 1.11–1.01 [m, 6 H, CH(C*H*$_3$)$_2$].

^{13}C NMR: δ = 149.7, 141.1, 129.3, 129.2 128.6, 127.4, 66.1, 36.4, 24.3, 22.2, 22.1.

GC–MS (t_R = 15.32 min): *m*/*z* = 190 (2) [M$^+$], 172 (5), 157 (25).

Anal. Calcd for $C_{13}H_{18}O$ (190.3): C, 82.06; H, 9.53. Found: C, 82.14; H, 9.47.

(*E*,*R*)-Acetic Acid-1,4-dimethyl-3-phenyl-2-pentenyl Ester [(*E*,*R*)-6] and (*E*,*S*)-5-Methyl-4-phenyl-3-hexen-2-ol [(*E*,*S*)-5]

To a stirred solution of compound (*E*)-(±)-**5** (102.6 g, 0.54 mol) in TBME (0.4 L) were added PS (50 g) and vinyl acetate (50 mL). After 9 d the suspension was filtered and the PS was recovered as it was and could be reused for several resolutions. The organic solution was concentrated under reduced pressure to obtain a yellow oil. Column chromatography of the crude material [SiO_2, hexane–EtOAc, (8:2)] yielded the compounds **5** and **6** in the following order.

(*E*,*R*)-6

Yield: 52.6 g (42%); 99.5% ee (vide infra); $[\alpha]_D^{20}$ = +116.1 (*c* = 1.03, $CHCl_3$).

^{1}H NMR: δ = 7.34–7.08 (m, 5 H, ArH), 5.83 (dq, *J* = 8.9, 6.2 Hz, 1 H, CHOAc), 5.25 (d, *J* = 8.9 Hz, 1 H, CH=), 3.11 [septuplet, *J* = 6.9 Hz, 1 H, C*H*$(CH_3)_2$], 2.04 (s, 3 H, $OCCH_3$), 1.37 [d, *J* = 6.2 Hz, 3 H, AcOCHC*H*$_3$], 1.01–1.13 [m, 6 H, CH(C*H*$_3$)$_2$].

^{13}C NMR: δ = 171.0, 150.5, 142.5, 133.4, 129.2 128.9, 128.1, 127.3, 67.8, 30.5, 22.6, 22.2, 22.0, 21.9.

GC–MS (t_R = 18.48 min): *m*/*z* = 232 (2) [M$^+$], 189 (70), 172 (20).

Anal. Calcd for $C_{15}H_{20}O_2$ (232.3): C, 77.55; H, 8.68. Found: C, 77.43; H, 8.80.

(*E*,*S*)-5

Yield: 58 g (47%); 92% ee by HPLC [(*R*)-isomer: t_R = 22.1 min, (*S*)-isomer: t_R = 44.9 min]; $[\alpha]_D^{20}$ = –20.8 (*c* = 1.01, $CHCl_3$).

Anal. Calcd for $C_{13}H_{18}O$ (190.3): C, 82.06; H, 9.53. Found: C, 82.24; H, 9.49.

(*E*,*R*)-5-Methyl-4-phenyl-3-hexen-2-ol [(*E*,*R*)-5]

To a solution of (*E*,*R*)-**6** (6.5 g, 28 mmol) in EtOH (20 mL) was added a solution of KOH (9 g, 0.16 mol) in water–EtOH (30 mL (7:3)]. After 4 h at refluxing temperature the reaction was poured into ice (200 mL) and neutralized with HCl (1 M), extracted with Et_2O (3 × 100 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure to give an oil which was passed on a pad of silica gel using hexane–EtOAc (75:25) affording the alcohol (*E*,*R*)-**5**; yield: 4.9 g (93%); colorless oil; 99.5% ee by HPLC; $[\alpha]_D^{20}$ = +22.9 (*c* = 1.12, $CHCl_3$).

Anal. Calcd for $C_{13}H_{18}O$ (190.3): C, 82.06; H, 9.53. Found: C, 82.12; H, 9.44.

(*E*,*S*)-3-Isopropyl-3-phenyl-4-hexenoic Acid [(*E*,*S*)-7]

To a solution of (*E*,*R*)-**5** (46 g, 0.24 mol) in triethylorthoacetate (TEOA; 0.6 L) placed in a 1 L round bottom flask equipped with a condenser/distillation head was added propionic acid (1 mL). The reaction mixture was heated to 150 °C and the EtOH was continuously collected. During the reaction, propionic acid was occasionally renewed. After 6–7 h the excess of TEOA was removed by distillation to yield an orange-colored oily residue. To a solution of the residue in EtOH–H_2O (0.5 L, 1:2) was added dropwise a solution of KOH (22 g, 0.39 mol) in H_2O (100 mL) and refluxed for 6 h. Most of TEOA was removed under reduce pressure and the residue was washed with Et_2O (2 × 200 mL) and dried over Na_2SO_4. The water solution was neutralized with HCl (1 M) and washed with CH_2Cl_2 (3 × 300 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure to give a yellow oil that was passed on a pad of silica gel using hexane–EtOAc (9:1) as eluent affording compound (*E*,*S*)-**7**; yield: 50.1 g (90%); colorless oil; $[\alpha]_D^{20}$ = +48.5 (*c* = 1.0, $CHCl_3$).

^{1}H NMR: δ = 8.65 (br s, 1 H, CO_2H), 7.35–7.06 (m, 5 H, ArH), 5.72 (dd, *J* = 15.4, 1.4 Hz, 1 H, C*H*=CHCH$_3$), 5.56 (m, 1 H, CH=C*H*CH$_3$), 2.81–2.64 (m, 2 × 1 H, CH_2), 2.48 [septuplet, *J* = 6.9 Hz, 1 H, C*H*(CH$_3$)$_2$], 1.82 (dd, *J* = 1.5, 5.5 Hz, 3 H, =CHC*H*$_3$), 0.84 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$), 0.76 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$).

^{13}C NMR: δ = 177.9, 144.8, 133.7, 128.6, 128.5, 126.7, 126.5, 50.2, 43.1, 34.4, 32.8, 19.1, 18.7, 18.5.

GC–MS (t_R = 21.63 min): *m*/*z* = 232 (2) [M$^+$], 189 (20), 143 (25).

Anal. Calcd for $C_{15}H_{20}O_2$ (232.33): C, 77.55; H, 8.68. Found: C, 77.66; H, 8.49.

(*E*,*R*)-3-Isopropyl-3-phenyl-4-hexenoic Acid [(*E*,*R*)-7]

The acid (*E*,*R*)-**7** was obtained following the same procedure as used for the synthesis of (*E*,*S*)-**7**.

$[\alpha]_D^{20}$ = –45.6.

Anal. Calcd for $C_{15}H_{20}O_2$ (232.33): C, 77.55; H, 8.68. Found: C, 77.71; H, 8.53.

(*E*,*S*)-Isopropyl-4-phenyl-5-hepten-2-one [(*E*,*S*)-8]

To an ice-cooled solution of (*E*,*S*)-**7** (38.9 g, 0.17 mol) and Et_3N (27.8 mL, 0.2 mol) in THF (0.3 L) was added dropwise a solution of chloroethyl formiate (19.2 mL, 0.2 mol) over 30 min. After 1 h the reaction mixture was concentrated under reduced pressure. The residue was triturated in Et_2O (200 mL) and the white solid was filtered. To this solution at –15 °C was added dropwise under a N_2 atmosphere a freshly prepared solution of MeMgI (Mg: 6.0 g, 0.25 mol, and MeI: 28.4 mL, 0.20 mol). After 1 h the reaction was quenched with NH_4Cl (sat., 0.3 L), neutralized with HCl (0.1 N), washed with Et_2O (2 × 0.2 L) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give an oil. Column chromatography of the crude with hexane–EtOAc (9:1) as eluent gave compound (*E*,*S*)-**8**; yield: 27.4 g (70%), colorless oil; $[\alpha]_D^{20}$ = +67.9 (*c* = 1.1, $CHCl_3$).

^{1}H NMR: δ = 7.34–7.09 (m, 5 H, ArH), 5.72 (dd, *J* = 15.6, 1.0 Hz, 1 H, C*H*=CHCH$_3$), 5.63–5.46 (m, 1 H, CH=C*H*CH$_3$), 2.86 (s, 2 H, CH_2), 2.48 [septuplet, *J* = 6.9 Hz, 1 H, C*H*(CH$_3$)$_2$], 1.82 (dd, *J* = 1.2, 6.0 Hz, 3 H, =CHC*H*$_3$), 1.63 (s, 3 H, COCH$_3$), 0.87 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$), 0.75 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$).

^{13}C NMR: δ = 209.1, 145.4, 133.8, 128.6, 128.5, 126.7, 126.5, 126.4, 51.7, 50.7, 34.3, 32.8, 19.1, 18.7, 18.5.

GC–MS (t_R = 20.31 min): *m*/*z* = 230 (2) [M$^+$], 187 (100), 145 (90), 129 (80).

Anal. Calcd for $C_{16}H_{22}O$ (230.35): C, 83.43; H, 9.68. Found: C, 83.56; H, 9.59.

(*E*,*R*)-Isopropyl-4-phenyl-5-hepten-2-one [(*E*,*R*)-8]

The ketone (*E*,*R*)-**8** was obtained following the same procedure as used for the synthesis of (*E*,*S*)-**8**.

Selected data for (*E*,*R*)-**8**; $[\alpha]_D^{20}$ = –62.5.

Anal. Calcd for $C_{16}H_{22}O$ (230.35): C, 83.43; H, 9.68. Found: C, 83.46; H, 9.64.

(*E*,2*RS*,4*S*)-Isopropyl-4-phenyl-5-hepten-2-ol [(*E*,2*RS*,4*S*)-9]

To an ice-cooled solution of (*E*,*S*)-**8** (29.7 g, 0.13 mol) in EtOH (0.3 L) was added $NaBH_4$ (7.6 g, 0.2 mol). After 4 h at r.t. the reaction mixture was quenched with sat. NH_4Cl (0.3 L), neutralized with HCl (1 M) and washed with CH_2Cl_2 (3 × 300 mL). The combined organic layers was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the alcohol (*E*,2*RS*,4*S*)-**9**; yield: 24.8 g (83%); yellow pale oil.

^{1}H NMR: δ = 7.35–7.08 (m, 2 × 5 H, ArH), 5.68–5.83 (m, 2 × 1 H, C*H*=CHCH$_3$), 5.53–5.41 (m, 2 × 1 H, CH=C*H*CH$_3$), 3.81–3.58 (m, 1 H, CHOH), 3.68–3.48 (m, 1 H, C*H*OH), 2.38–2.25 [m, 2 × 1 H, C*H*(CH$_3$)$_2$], 2.14 (dd, *J* = 1.4, 13.3 Hz, 1 H, C*H*CHOH), 2.04 (dd, *J* = 7.4, 14.8 Hz, 1 H, C*H*CHOH), 1.82 (m, 1 H, 2 × 3 H, C*H*CHOH, =CHC*H*$_3$), 1.75 (dd, *J* = 7.9, 14.9 Hz, 1 H, C*H*CHOH), 1.30 (br s, 1 H, OH), 1.18 (br s, 1 H, OH), 1.08 (d, *J* = 6.4 Hz, 3 H, OHCHC*H*$_3$), 0.96 (d, *J* = 6.4 Hz, 3 H, OHCHC*H*$_3$), 0.97–0.81 (m, 2 × 3 H, CHC*H*$_3$), 0.74 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$), 0.71 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$).

^{13}C NMR: δ = 146.1, 145.8, 134.7, 133.6, 129.0, 128.8, 128.6, 128.5, 127.2, 126.9, 126.7, 126.5, 66.0, 65.9, 51.0, 50.8, 48.01, 47.7, 36.2, 36.2, 25.0, 24.9, 19.2, 19.16, 18.9, 18.7, 18.5, 18.4.

GC–MS (t_R = 20.36 min): *m*/*z* = 232 (2) [M$^+$], 189 (10), 145 (100), 129 (15).

(*E*,2*RS*,4*R*)-Isopropyl-4-phenyl-5-hepten-2-ol [(*E*,2*RS*,4*R*)-9]

The alcohols (*E*,2*RS*,4*R*)-**9** were obtained following the same procedure used for the synthesis of (*E*,2*RS*,4*S*)-**9**.

(*E*,1*RS*,3*S*)-Acetic Acid 3-Isopropyl-1-methyl-4-hexenyl Ester [(*E*,1*RS*,3*S*)-10]

To a solution of alcohols (*E*,2*RS*,4*S*)-**9** (16.2 g, 0.07 mol) in pyridine (100 mL) was added Ac_2O (20 mL). The reaction mixture after 12 h was worked in the usual way to afford the acetates (*E*,1*R*,3*RS*)-**10** which was used without further purification for the next step; yield: 19.0 g (99%); yellow oil.

^{1}H NMR: δ = 7.34–7.04 (m, 2 × 5 H, ArH), 5.71–5.40 (m, 3 × 1 H, CHOAc, C*H*=CHCH$_3$), 4.87–4.71 (m, 1 H, CHOAc), 2.44–2.21 [m, 2 × 1 H, C*H*(CH$_3$)$_2$], 2.05 (dd, *J* = 7.8, 14.9 Hz, 1 H, C*H*CHOAc), 1.96 (dd, *J* = 1.7, 14.9 Hz, 1 H, C*H*CHOAc), 1.88–1.79 (m, 2 × 1 H, 2 × 3, C*H*CHOAc, =CCH$_3$), 1.73 (s, 3 H, COCH$_3$), 1.52 (s, 3 H, COCH$_3$), 1.06 (d, *J* = 6.3 Hz, 3 H, AcOCHC*H*$_3$), 0.95 (d, *J* = 6.4 Hz, 3 H, AcOCHC*H*$_3$), 0.87 (d, *J* = 6.6 Hz, 3 H, CHC*H*$_3$), 0.83 (d, *J* = 6.6 Hz, 3 H, CHC*H*$_3$), 0.77 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$), 0.69 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$).

^{13}C NMR: δ = 170.1, 145.0, 144.9, 133.6, 132.9, 128.2, 128.1, 127.8, 127.7, 125.8, 125.7, 125.5, 125.4, 68.4, 50.1, 49.8, 43.9, 43.6, 35.0, 33.8, 21.9, 21.8, 21.2, 20.6, 18.3, 17.8, 17.7.

GC–MS [t_R = 21.57 min (I diast.)]: *m*/*z* = 230 (5) [M – 44], 171 (100), 143 (20).

GC–MS [t_R = 21.65 min (II diast.)]: *m*/*z* = 230 (10) [M – 44], 171 (100), 143 (20).

(*E*,1*RS*,3*S*)-Acetic Acid 3-Isopropyl-1-methyl-4-hexenyl Ester [(*E*,1*RS*,3*R*)-10]

The esters (*E*,1*RS*,3*R*)-**10** were obtained following the same procedure as used for the synthesis of (*E*,1*RS*,3*S*)-**10**.

(1*S*,3*R*)-Acetic Acid 3-Formyl-1,4-dimethyl-3-phenylpentyl Ester [(1*S*,3*R*)-11] and (1*R*,3*R*)-Acetic Acid 3-Formyl-1,4-dimethyl-3-phenylpentyl Ester [(1*R*,3*R*)-11]

After the ozonolysis of a solution of (*E*,1*RS*,3*S*)-**10** (18 g, 66 mmol) in CH_2Cl_2–MeOH (0.3 L, 2:1) at –78 °C was completed, the reaction mixture was treated with a solution of PPh_3 (25 g) in CH_2Cl_2 (100 mL). At r.t. the reaction mixture was concentrated under reduce pressure affording a yellow white solid. The crude material was passed through a pad of silica gel. Column chromatography of the residue with eluent hexane–EtOAc (9:1) yielded the aldehyde.

(1*S*,3*R*)-11

Yield: 5.9 g (34%); colorless oil; $[\alpha]_D^{20} = -24.4$ ($c = 0.95$, $CHCl_3$).

^{1}H NMR: δ = 9.81 (s, 1 H, OCH), 7.40–7.08 (m, 5 H, ArH), 4.90–4.79 (m, 1 H, CHOAc), 2.43 [septuplet, $J = 6.9$ Hz, 1 H, C*H*$(CH_3)_2$], 2.25 (dd, $J = 2.7$, 15.0 Hz, 1 H, C*H*CHOAc), 2.13 (dd, $J = 9.2$, 15.0 Hz, 1 H, C*H*CHOAc), 1.73 (s, 3 H, $COCH_3$), 1.17 (d, $J = 6.2$ Hz, 3 H, AcOCHC*H*$_3$), 0.91 (d, $J = 7.0$ Hz, 3 H, CHC*H*$_3$), 0.84 (d, $J = 6.9$ Hz, 3 H, CHC*H*$_3$).

^{13}C NMR: δ = 203.6, 170.1, 137.7, 128.6, 128.3, 127.2, 67.7, 59.3, 39.5, 31.7, 21.6, 20.8, 18.5, 17.8.

Anal. Calcd for $C_{16}H_{22}O_3$ (262.35): C, 73.25; H, 8.45. Found: C, 73.36; H, 8.59.

(1*R*,3*R*)-11

Yield: 4.8 g (28%); white needles; mp 52 °C; $[\alpha]_D^{20} < 1$ ($c = 1.01$, $CHCl_3$).

^{1}H NMR: δ = 9.83 (s, 1 H, OCH), 7.41–7.08 (m, 5 H, ArH), 4.84–4.65 (m, 1 H, CHOAc), 2.44 [septuplet, $J = 7.0$ Hz, 1 H, C*H*$(CH_3)_2$], 2.32 (dd, $J = 9.6$, 15.2 Hz, 1 H, C*H*CHOAc), 2.16 (dd, $J = 2.5$, 15.2 Hz, 1 H, C*H*CHOAc), 1.78 (s, 3 H, $COCH_3$), 1.17 (d, $J = 6.2$ Hz, 3 H, AcOCHC*H*$_3$), 0.94–0.86 [m, 2 × 3 H, CH(C*H*$_3)_2$].

^{13}C NMR: δ = 204.0, 169.8, 137.8, 128.4, 128,3, 127.0, 67.7, 58.8, 40.8, 33.7, 21.3, 21.0, 18.2, 17.8.

GC–MS (for both isomers: $t_R = 21.80$ min): $m/z = 174$ (30) [M^+ – 88], 160 (20), 145 (25), 131 (100).

Anal. Calcd for $C_{16}H_{22}O_3$ (262.35): C, 73.25; H, 8.45. Found: C, 73.39; H, 8.49.

(1*S*,3*S*)-Acetic Acid 3-Formyl-1,4-dimethyl-3-phenylpentyl Ester (1*S*,3*S*)-11 and (1*R*,3*S*)-Acetic Acid 3-Formyl-1,4-dimethyl-3-phenylpentyl Ester (1*R*,3*S*)-11

The aldehydes (1*R*,3*S*)-**11** and (1*S*,3*S*)-**11** were obtained following the above procedure.

(1*R*,3*S*)-11

Colorless oil; $[\alpha]_D^{20} = +22.4$ ($c = 1.1$, $CHCl_3$).

Anal. Calcd for $C_{16}H_{22}O_3$ (262.35): C, 73.25; H, 8.45. Found: C, 73.29; H, 8.48.

(1*S*,3*S*)-11

White powder; $[\alpha]_D^{20} < -1$ ($c = 1.2$, $CHCl_3$).

Anal. Calcd for $C_{16}H_{22}O_3$ (262.35): C, 73.25; H, 8.45. Found: C, 73.32; H, 8.51.

(2*R*,4*S*)-4-Hydroxy-2-isopropyl-2-phenylpentanenitrile [(2*R*,4*S*)-12] and (3*R*,5*S*)-3-Isopropyl-5-methyl-3-phenyldihydrofuran-2-one [(3*S*,5*R*)-13]

To a solution of aldehyde (1*S*,3*R*)-**11** (8.2 g, 30.5 mmol) in EtOH (50 mL) were added NaOAc (3.6 g, 45.8 mmol) and $NH_2OH{\cdot}HCl$ (3.2 g, 45.8 mmol). After 24 h, the reaction was quenched with water (50 mL) and washed Et_2O (2 × 150 mL), the combined organic layers were washed with $NaHCO_3$ (2 × 50 mL) and then dried over Na_2SO_4. The solvent was removed under reduced pressure affording the oxime as a yellow oil that was used in the next step without further purification. A solution of this crude material in Ac_2O (50 mL) was refluxed for 6 h and then concentrated at reduced pressure. The solution of the residue in Et_2O was washed with HCl (0.1 M, 2 × 50 mL) and with sat. $NaHCO_3$ (50 mL), dried over Na_2SO_4. The solvent was removed under reduced pressure to give a yellow oil. To an ice-cooled solution of the latter in EtOH (150 mL) was added dropwise a solution of KOH (1.5 g) in water–EtOH (30 mL, 7:3). After 4 h the reaction mixture was poured into ice (200 mL) and neutralized with HCl (1 M), extracted with Et_2O (3 × 100 mL), dried over Na_2SO_4. The solvent was removed under reduced pressure to yield an oil. Column chromatography of the crude material (SiO_2, hexane–EtOAc, 8:2) gave the compound **12** and **13** in the following order.

(3*R*,5*S*)-13

Yield: 1.2 g (18%); pale yellow oil; $[\alpha]_D^{20} = -88.0$ ($c = 1.42$, $CHCl_3$).

^{1}H NMR: δ = 7.70 (d, $J = 7.6$ Hz, 2 H, ArH), 7.41–7.09 (m, 3 H, ArH), 4.56–4.43 (m, 1 H, OCHMe), 2.63 (dd, $J = 7.6$, 13.4 Hz, 1 H, HC*H*CHMe), 2.32–2.21 [m, 2 × 1 H, HCC*H*Me, C*H*$(CH_3)_2$], 1.18 (d, $J = 6.8$ Hz, 3 H, CH_2CHCH_3), 0.96 (d, $J = 6.8$ Hz, 3 H, CHC*H*$_3$), 0.87 (d, $J = 6.8$ Hz, 3 H, CHC*H*$_3$).

^{13}C NMR: δ = 174.6, 143.1, 137.8, 128.0, 127.3, 126.5, 74.7, 40.2, 33.4, 22.1, 18.8, 18.1.

GC–MS ($t_R = 20.32$ min): $m/z = 218$ (10) [M^+], 160 (20), 145 (25), 131 (100).

(2*R*,4*S*)-12

Yield: 1.7 g (25%); colorless oil; $[\alpha]_D^{20} = +10.0$ ($c = 1.22$, $CHCl_3$).

^{1}H NMR: δ = 7.52–7.23 (m, 5 H, ArH), 3.74–3.62 (m, 1 H, HOC*H*Me), 2.21–2.08 [m, 2 H, 1 H, C*H*$_2$CHOH, C*H*$(CH_3)_2$], 1.18 (d, $J = 6.8$ Hz, 6 H, CHC*H*$_3$, CH_2CHCH_3), 0.72 (d, $J = 6.8$ Hz, 3 H, CHC*H*$_3$).

^{13}C NMR: δ = 137.7, 129.1, 128.1, 126.5, 120.9, 52.2, 46.9, 38.4, 24.0, 18.6, 18.5.

GC–MS ($t_R = 20.76$ min): $m/z = 218$ (5) [M], 201 (15), 145 (25), 131 (100).

Anal. Calcd for $C_{14}H_{19}NO$ (217.31): C, 77.38; H, 8.81; N, 6.45. Found: C, 77.36; H, 8.69; N, 6.33.

(2*R*,4*R*)-4-Hydroxy-2-isopropyl-2-phenylpentanenitrile [(2*R*,*R*)-12] and (3*R*,5*R*)-3-Isopropyl-5-methyl-3-phenyldihydrofuran-2-one [(3*R*,5*R*)-13]

The lactone (3*R*,5*R*)-**13** and the nitrile (2*R*,4*R*)-**12** were obtained following the above procedure starting from aldehyde (1*R*,3*R*)-**11**.

(3*R*,5*R*)-13

Yield: 0.9 g (22%); colorless oil; $[\alpha]_D^{20} = -45.3$ ($c = 1.17$, $CHCl_3$).

^{1}H NMR: δ = 7.72 (d, $J = 7.6$ Hz, 2 H, ArH), 7.41–7.14 (m, 3 H, ArH), 4.31–4.20 (m, 1 H, OC*H*Me), 2.62 (dd, $J = 4.6$, 13.0 Hz, 1 H, HC*H*CHMe), 2.36 [septuplet, $J = 6.9$ Hz, 1 H, C*H*$(CH_3)_2$], 1.94 (dd, $J = 10.9$, 13.0 Hz, 1 H, HC*H*CHMe), 1.35 (d, $J = 6.0$ Hz, 3 H, CH_2CHCH_3), 1.06 (d, $J = 6.9$ Hz, 3 H, CHC*H*$_3$), 0.73 (d, $J = 6.9$ Hz, 3 H, CHC*H*$_3$).

^{13}C NMR: δ = 174.3, 140.1, 128.4, 127.0, 126.9, 126.5, 73.9, 57.2, 37.1, 35.4, 20.5, 18.7, 18.3.

GC–MS ($t_R = 20.33$ min): $m/z = 218$ (15) [M^+], 160 (20), 145 (25), 131 (100).

(2*R*,4*R*)-12

Yield: 1.2 g (29%); colorless oil; $[\alpha]_D^{20} = -22.0$ ($c = 1.12$, $CHCl_3$).

^{1}H NMR: δ = 7.52–7.18 (m, 5 H, ArH), 3.54–3.40 (m, 1 H, HOCHMe), 2.35 (dd, $J = 9.0$, 14.4 Hz, 1 H, HC*H*CHMe), 2.13 [sep-

tuplet, J = 6.9 Hz, C*H*(CH_3)$_2$], 1.93 (dd, J = 2.7, 14.4 Hz, 1 H, HC*H*-CHMe), 1.60 (br d, J = 9.1 Hz, 1 H, OH), 1.23 (d, J = 6.6 Hz, 3 H, CH_2CHC*H*$_3$), 1.04 (d, J = 6.9 Hz, 3 H, CHC*H*$_3$), 0.77 (d, J = 6.9 Hz, 3 H, CHC*H*$_3$).

^{13}C NMR: δ = 138.0, 128.8, 127.7, 126.5, 65.0, 51.2, 47.0, 38.5, 24.4, 18.6, 18.5.

GC–MS (t_R = 20.18 min): m/z = 217 (30) [M$^+$], 200 (15), 160 (20), 145 (25), 131 (100).

Anal. Calcd for $C_{14}H_{19}NO$ (217.31): C, 77.38; H, 8.81; N, 6.45. Found: C, 77.41; H, 8.79; N, 6.38.

(2*S*,4*S*)-4-Hydroxy-2-isopropyl-2-phenylpentanenitrile [(2*S*,4*S*)-12] and (3*S*,5*S*)-3-Isopropyl-5-methyl-3-phenyldihydrofuran-2-one [(3*S*,5*S*)-13]

The lactone (3*S*,5*S*)-**13** and the nitrile (2*S*,4*S*)-**12** were obtained following the above procedure starting from aldehyde (1*S*,3*S*)-**11**.

(3*S*,5*S*)-13

Yellow pale oil; $[\alpha]_D^{20}$ = +43 (c = 1.32, $CHCl_3$).

(2*S*,4*S*)-12

Colorless oil; $[\alpha]_D^{20}$ = +21.4 (c = 1.05, $CHCl_3$).

Anal. Calcd for $C_{14}H_{19}NO$ (217.31): C, 77.38; H, 8.81; N, 6.45. Found: C, 77.31; H, 8.79; N, 6.47.

(2*S*,4*R*)-4-Hydroxy-2-isopropyl-2-phenylpentanenitrile [(2*S*,4*R*)-12] and (3*S*,5*R*)-3-Isopropyl-5-methyl-3-phenyldihydrofuran-2-one [(3*S*,5*R*)-13]

The lactone (3*S*,5*R*)-**13** and the nitrile (2*S*,4*R*)-**12** were obtained following the above procedure starting from aldehyde (1*S*,3*R*)-**11**.

(3*S*,5*R*)-13

Yellow pale oil; $[\alpha]_D^{20}$ = +86 (c = 1.32, $CHCl_3$).

(2*S*,4*R*)-12

Colorless oil; $[\alpha]_D^{20}$ = –8.5 (c = 1.05, $CHCl_3$).

Anal. Calcd for $C_{14}H_{19}NO$ (217.31): C, 77.38; H, 8.81; N, 6.45. Found: C, 77.41; H, 8.73; N, 6.37.

(2*R*,4*R*)-4-Dimethylamino-2-isopropyl-2-phenylpentanenitrile [(2*R*,4*R*)-1]

To a solution of alcohol (2*R*,4*S*)-**12** (1.1 g, 5.1 mmol) in pyridine (20 mL) was added TsCl. After 12 h the reaction mixture was concentrated under reduced pressure, diluted in Et_2O (50 mL), then washed with HCl (0.1 M, 2 × 50 mL) and $NaHCO_3$ (2 × 50 mL). The reaction mixture was then concentrated under reduced pressure affording the tosylate derivative as a yellow oil that was used in the next step without further purification. To a solution of the tosylate in *i*-PrOH (30 mL) in a steel vessel was added a water solution of $NH(Me)_2$ (40%, 40 mL). After 24 h at 120 °C the reaction mixture was concentrated under reduced pressure. The solution of the residue in EtOAc was washed HCl (1 M, 2 × 25 mL), the combined water solution was neutralized with NaOH (0.1 M) and washed with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure affording a yellow white crystalline solid. Crystallization in hexane at low temperature yielded the amine (1*R*,3*R*)-**1**; yield: 0.65 g (52%); yellow prisms; mp 78 °C; $[\alpha]_D^{20}$ = –33.2 (c = 0.9, $CHCl_3$).

^{1}H NMR: δ = 7.52–7.20 (m, 5 H, ArH), 2.34 [dd, J = 2.4, 14.1 Hz, 1 H, HC*H*CHN(CH_3)$_2$], 2.22–2.10 [m, 2 × 1 H, C*H*N(CH_3)$_2$, C*H*(CH_3)$_2$], 2.03 [s, 6 H, N(CH_3)$_2$], 1.61 [dd, J = 4.7, 14.1 Hz, 1 H, HC*H*CHN(CH_3)$_2$], 1.23 (d, J = 6.6 Hz, 3 H, CH_2CHC*H*$_3$), 0.75 (d, J = 6.9 Hz, 3 H, CHC*H*$_3$), 0.63 (d, J = 6.9 Hz, 3 H, CH_3).

^{13}C NMR: δ = 138.8, 127.4, 126.3, 125.5, 121.1, 54.5, 50.9, 41.1, 38.7, 37.5, 17.8, 17.5, 11.5.

GC–MS (t_R = 21.13 min): m/z = 244 (2) [M$^+$], 229 (10), 158 (2), 72 (100).

Anal. Calcd for $C_{16}H_{24}N_2$ (244.38): C, 78.64; H, 9.90; N, 11.64. Found: C, 78.66; H, 9.92; N, 11.61.

(2*R*,4*S*)-4-Dimethylamino-2-isopropyl-2-phenylpentanenitrile [(2*R*,4*S*)-1]

The amine (2*R*,4*S*)-**1** was obtained following the above procedure starting from alcohol (2*R*,4*R*)-**12**; yield: 0.5 g (49%); yellow oil; $[\alpha]_D^{20}$ = –10.43 (c = 0.95, $CHCl_3$).

^{1}H NMR: δ = 7.42–7.21 (m, 5 H, ArH), 2.35–2.23 [m, 1 H, HC*H*CHN(CH_3)$_2$], 2.10–2.01 [m, 9 H, N(CH_3)$_2$, C*H*N(CH_3)$_2$, C*H*(CH_3)$_2$, HC*H*CHN(CH_3)$_2$], 1.22 (d, J = 6.6 Hz, 3 H, CH_2CHC*H*$_3$), 1.06 (d, J = 6.7 Hz, 3 H, CHC*H*$_3$), 0.74 (d, J = 6.7 Hz, 3 H, CHC*H*$_3$).

^{13}C NMR: δ = 138.2, 128.9, 127.8, 126.8, 121.6, 56.3, 51.5, 41.6, 40.1, 39.6, 19.0, 18.7, 13.8.

GC–MS (t_R = 21.06 min): m/z = 244 (2) [M$^+$], 229 (10), 158 (7), 72 (100).

Anal. Calcd for $C_{16}H_{24}N_2$ (244.38): C, 78.64; H, 9.90; N, 11.64. Found: C, 78.58; H, 9.96; N, 11.64.

(2*S*,4*S*)-4-Dimethylamino-2-isopropyl-2-phenylpentanenitrile [(2*S*,4*S*)-1]

The amine (2*S*,4*S*)-**1** was obtained following the above procedure starting from alcohol (2*S*,4*R*)-**12**.

Yellow powder; $[\alpha]_D^{20}$ = +32.2 (c = 0.97, $CHCl_3$).

Anal. Calcd for $C_{16}H_{24}N_2$ (244.38): C, 78.64; H, 9.90; N, 11.64. Found: C, 78.57; H, 9.92; N, 11.74.

(2*S*,4*R*)-4-Dimethylamino-2-isopropyl-2-phenylpentanenitrile [(2*S*,4*R*)-1]

The amine (2*S*,4*R*)-**1** was obtained following the above procedure starting from alcohol (2*S*,4*S*)-**12**.

Yellow oil; $[\alpha]_D^{20}$ = +10.13 (c = 1.2, $CHCl_3$).

Anal. Calcd for $C_{16}H_{24}N_2$ (244.38): C, 78.64; H, 9.90; N, 11.64. Found: C, 78.67; H, 9.92; N, 11.72.

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