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Biocatalysed synthesis of the enantiomers of the floral odorant Florhydral®

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Abstract—The two enantiomers of the floral odorant Florhydral® were prepared by enzymatic methods, and their olfactory properties were evaluated. (+)-Florhydral® was found to be much more powerful than the (−)-enantiomer.

1. Introduction

In the field of fragrance chemistry great effort is now devoted to the discovery of new molecules with interesting odour profiles, and to the preparation of known chiral odorant compounds as pure stereomers. The latter investigation is aimed to compare the odour properties of the single isomers, in order to verify whether they elicit different olfactory sensations, and to determine their threshold of perception. It would be possible to use only the olfactorally active isomer of a certain fragrance in perfume compositions, in order to reduce the quantity of chemicals employed and abate the correlated health and environmental risks. The *chiral switch* protocol has prompted patents claiming the odour properties of single isomers,[1] and stereoisomerically enriched odorants (i.e. Dextro-Norlimbanol®,[2] Hedione HC®,[3]) have been introduced on the market.

The preparation of perfume compositions with a delicate marine and watery touch is a new trend in modern perfumery.[4] 3-(3-Isopropylphenyl)butanal **1**, commercialised by Givaudan with the trade name of Florhydral®,[5] is a synthetic odorant employed to convey the fresh marine and ozonic note. It is described to have a fine floral, melon odour, with those qualities found in the lily-of-the-valley and linden blossom. It is powerful and diffusive, and it can be used to give long lasting fresh and green top notes. The two enantiomers of **1** have never been prepared in pure form. We describe herein the enzyme-mediated synthesis of (+)- and (−)-**1**, in order to obtain enantiopure samples for olfactory evaluation.

2. Results and discussions

Over the last few years we have shown the efficiency of lipase-mediated kinetic resolutions for the preparation of chiral odorant compounds in enantiopure form.[6] This enzymatic procedure is well suited for the resolution of sparingly functionalised molecules, such as those employed as odorants, and has the additional advantage of giving access to both enantiomers.

In a first approach to (+)- and (−)-**1**, racemic alcohol **2**, obtained by $NaBH_4$ reduction of commercial Florhydral®, was subjected to lipase-mediated transesterification. The reactions were carried out in *t*-butyl methyl ether solution in the presence of vinyl acetate, employing three different enzyme preparations (PPL, CRL, Lipase PS). Acetate **3a** (the first eluting enantiomer in chiral HPLC) was invariably obtained with low enantiomeric excess (e.e.) values: (i) PPL: e.e. **3a** = 69%, c[7] = 9%, after 2 h; e.e. **3a** = 24%, c = 43%, after 24 h; (ii) CRL: e.e. **3a** = 33%, c = 10%, after 2 h; e.e. **3a** = 11%, c = 71%, after 24 h; (iii) Lipase PS: e.e. **3a** = 60%, c = 11%, after 120′; e.e. **3a** = 0%, c = 100%, after 24 h.

It was thus decided to investigate the biocatalysed transesterification of the racemic alcohol (±)-**4**, with the hydroxy group to be acetylated nearer to the stereo-

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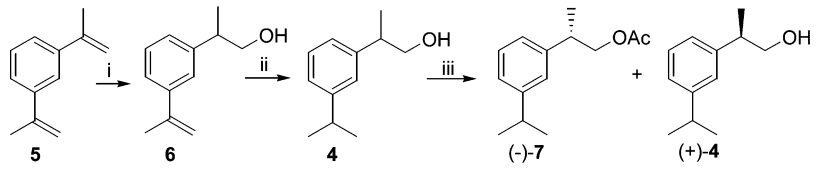
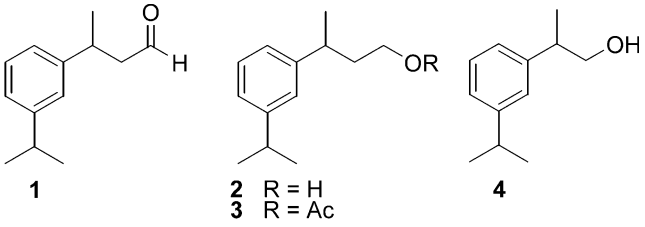


Scheme 1. (i) $BH_3(CH_3)_2S$, THF; then $NaOH–H_2O_2$; (ii) H_2, Pd/C; (iii) PPL, *t*-butylmethyl ether, vinyl acetate; column chromatography.

genic centre, in the hope of observing higher enantioselectivity. The preparation of racemic **4** is shown in Scheme 1. Hydroboration of 1,3-diisopropenyl benzene **5** was performed under controlled reaction conditions, and gave after quenching of the mixture with $NaOH–H_2O_2$, the alcohol **6**. The alkene group of **6** was reduced by hydrogenation in the presence of Pd/C in ethyl acetate solution, to afford alcohol **4** in very good overall yield.

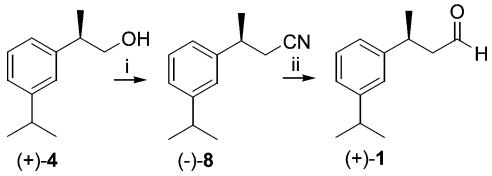


Lipase-mediated transesterification of **4** (*t*-butylmethyl ether, vinyl acetate, room temperature) was investigated in the presence of PPL, CRL, and Lipase PS: after 24 h acetate (–)-**7** (the first eluting enantiomer in chiral GC) was obtained with the following e.e. values: PPL e.e. = 81%; CRL e.e. = 50%; Lipase PS e.e. = 33%. PPL-mediated acetylation was investigated for a longer reaction time, in order to verify whether the e.e. was maintained at higher conversion. After 96 h, acetate (–)-**7** (e.e. = 60%, chiral GC) and unreacted alcohol (+)-**4** (e.e. = 55%, chiral GC of the corresponding acetate) were recovered (C = 48%, $E = 6.8$). The enantiomeric excess of (+)-**4** was increased by repeating the enzymatic transesterification reaction. After 120 h reaction time, alcohol (+)-**4** was recovered with e.e. of >99%. Acetate (–)-**7** (e.e. = 60%) was hydrolysed with KOH in methanol, and the corresponding alcohol (–)-**4** was submitted to enzymatic acetylation. After 48 h, acetate (–)-**7** with e.e. of >99% was obtained.

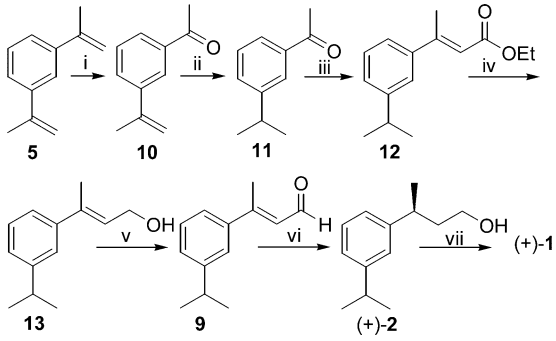
The enantiopure alcohols (+)- and (–)-**4** were then employed as starting materials in the preparation of the enantiomeric Florhydrals®. They were treated separately with *p*-toluenesulphonyl chloride in pyridine, and the corresponding tosylate derivatives were submitted directly, without further purification, to cyanide displacement (Scheme 2). Compounds (–)- and (+)-**8** were thus recovered and reduced with diisobutylaluminum hydride in THF at −10°C, to afford enantiopure (+)- and (–)-**1**, respectively.

The two enantiopure samples of (+)- and (–)-**1** were then submitted to skilled perfumers (Givaudan) for olfactory evaluation and the following descriptions were obtained: (+)-**1** was found to be floral, watery, green, yet with an acidic touch, even in the dry down note. In comparison with racemic **1**, the (+)-enantiomer has a more green, less watery, and more powerful fragrance (odour threshold = 0.035 ng/l air). The (–)-enantiomer has a typical Florhydral® smell, floral, fresh, green, muguet-like, but more marine, and more plastic (odour threshold = 0.88 ng/l air).

(+)-**1** was found to be the most potent of the two enantiomers of Florhydral®, and thus an enzymatic method was required to produce it by enantiospecific synthesis. Baker's yeast (BY)-mediated reduction of double bonds, carboxylic acid and carbonyl groups is well documented in the literature.[8] We have exploited this approach in the past for the preparation of fragrant molecules, such as rose oxide,[9] and Aerangis lactone.[10] Thus it was decided to investigate a BY-mediated route to enantiomerically enriched **1**. We prepared unsaturated aldehyde **9**, according to the sequence reported in Scheme 3. Ozonolysis of 1,3-diisopropenylbenzene under strictly controlled conditions gave, after quenching the reaction mixture with PPh_3, unsaturated ketone derivative **10**, subsequent hydrogenation afforded ketone **11**, which was condensed with (triphenyl-λ^5-phosphanylidene)acetic acid ethyl ester, to afford unsaturated ester **12** ($E/Z = 10:1$, ^1H NMR).



Scheme 2. (i) TosCl, pyridine; then NaCN in DMSO; (ii) diisobutylaluminum hydride in THF.



Scheme 3. (i) O_3 in CH_2Cl_2–MeOH, then PPh_3; (ii) H_2, Pd/C; (iii) PPh_3=CHCOOEt in toluene; (iv) Red-Al in toluene; (v) MnO_2 in CH_2Cl_2; (vi) Baker's yeast; (vii) PCC in CH_2Cl_2.

Reduction with Red-Al in toluene, and MnO_2 oxidation of the resulting allylic alcohol **13** ($E/Z=10:1$, ^1H NMR) allowed us to obtain unsaturated aldehyde **9** ($E/Z=5:1$, ^1H NMR). After 48 h of BY fermentation, complete consumption of (*E*)- and (*Z*)-**9** was observed. The alcohol fraction recovered from the reaction mixture showed the following composition (GC/MS): saturated alcohol **2** (49%), (*Z*)-**13** (21%) and (*E*)-**13** (30%). This product mixture was treated with MnO_2 in refluxing methylene chloride, to give, after removal of the unsaturated aldehyde by column chromatography, saturated alcohol (+)-**2** in pure form, with e.e. = 97% (HPLC). The high enantiomeric excess of (+)-**2**, in spite of the presence of the (*Z*)-isomer of the starting aldehyde **9**, can be justified on the basis that only the double bond of intermediate (*E*)-**13** was microbially reduced. It is known that the BY-reduction of (*E*)- and (*Z*)-3-aryl-alk-2-enals affords the two opposite enantiomers of the corresponding 3-aryl-alkanols.[11]

Derivative (+)-**2** was oxidised with PCC to afford (+)-**1**. The BY-mediated synthesis was thus found to be enantiospecific, providing the most potent enantiomer of Florhydral®.

We tentatively assigned (*S*)-configuration to acetate (−)-**7** on the basis of literature data regarding structurally correlated substrates. It is known that the (*S*)-enantiomers of racemic 2-arylalkan-1-ols (primary alcohols) are preferentially acetylated by lipases (PPL, CRL, Lipase PS) under various experimental conditions.[12] This assignment is in agreement with the recovery of (*S*)-**2** from BY fermentation of **9**, as it is generally observed that (*E*)-3-aryl-alk-2-enals are reduced by BY to give (*S*)-3-aryl-alkanols.[11] The same enantiomer of Florhydral® was obtained from alcohol (+)-**4** left unreacted by lipases and from derivative (+)-**2** prepared by BY reduction.

3. Conclusions

The enantiomers of the floral odorant Florhydral® were obtained in enantiopure form, according to a procedure involving lipase-catalysed acetylation. Each enantiomer was submitted to olfactory evaluation and (+)-**1** was found to be the most powerful isomer with odorant properties. It was subsequently prepared by enantiospecific synthesis involving BY-mediated reduction as a key step.

This work shows that lipase-catalysed kinetic resolution is a very efficient procedure for the preparation of both enantiomers of sparingly functionalised molecules, such as (+)- and (−)-**4**. Enantioselective BY fermentations allow the preparation of only one enantiomer of the desired chiral compound. The stereochemical course of BY-mediated reduction of carbonyl groups can be controlled,[8] but that of double bond saturation cannot be modified. However, it can be more convenient to prepare just one enantiomer of a certain chiral compound, the most active one, in order to increase the yield of transformation of the starting material, and avoid production of the useless isomer. As in this case, BY can be greatly useful in producing the desired enantiomer.

4. Experimental

Porcine pancreatic lipase (PPL type II, Sigma), *Candida rugosa* lipase (CRL, Sigma), *Burkholderia cepacia* lipase (Lipase PS, Amano Pharmaceuticals Co., Japan) were employed in this work. 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 μm). The following temperature program was employed: 60°C (1 min)/6°/min/150° (1 min)/12°/min/280° (5 min). Chiral HPLC analyses of compounds **3a**, **3b**, (−)-**2**, and (+)-**2** were performed on a Chiralcel OD column (Daicel-Japan) installed on a Merck-Hitachi L-6200 apparatus: 0.6 mL/min, UV detector (254 nm), hexane/isopropanol 95:5. The following retention times were observed: **3a** (acetyl derivatives of (+)-**2**) $t_R=6.32$ min; **3b** (acetyl derivatives of (−)-**2**) $t_R=6.95$ min; (−)-**2** $t_R=10.20$ min; (+)-**2** $t_R=10.59$ min. Chiral GC analyses of derivative **7** were performed on a Chirasil DEX CB, 25 m×0.25 mm (Chrompack) column, installed on a DANI HT 86.10 gas chromatograph, with the following temperature program: 50°C (3′)-8°C/min-100°C (30′)-8°C/min-180°C (1′). The following retention times were observed: (−)-**7** $t_R=35.3$ min, (+)-**7** $t_R=35.8$ min. ^1H NMR spectra were recorded at room temperature on a Bruker AC-250 spectrometer (250 MHz ^1H). The chemical shift scale was based on internal tetramethylsilane. Optical rotations were measured on a Dr. Kernchen Propol digital automatic polarimeter. Microanalyses were determined on a Analyzer 1106 Carlo Erba. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. All the chromatographic separations were carried out on silica gel columns.

4.1. 2-(3-Isopropenylphenyl)propan-1-ol 6

To a solution of diisopropenylbenzene (50.0 g, 0.32 mol) in THF (300 mL), a solution of $BH_3{\cdot}(CH_3)_2S$ (10 M, 35 mL, 0.35 mol) was added at 0°C. The reaction mixture was stirred at room temperature for 1 h, then treated with NaOH (1.05 mol) and H_2O_2 (108 mL, 1.05 mol). The mixture was poured into water, extracted with diethyl ether, and dried (Na_2SO_4). The solution was concentrated under reduced pressure, and the residue was purified by column chromatography, eluting with hexane/ethyl acetate 8:2, to afford compound **6** (30.6 g, 55%); ^1H NMR: δ 7.38–7.10 (4H, m, aromatic hydrogens), 5.36 (1H, *m*, C*H*H=C), 5.09 (1H, *m*, C*H*H=C), 3.60 (2H, d, $J=6.9$, CH_2OH), 2.95 (1H, m, CH_3CH), 2.15 (3H, m, CH_3C=), 1.27 (3H, d, $J=6.9$, CH_3CH); GC/MS: $t_R=17.05$ min; m/z: 176 (M^+, 40), 158 (5), 145 (100).

4.2. 2-(3-Isopropylphenyl)propan-1-ol 4

Compound **6** (30.0 g, 0.17 mol) was hydrogenated in the presence of 5% Pd/C (3.0 g) in ethyl acetate solution (200 mL). After the usual work-up, the residue was

chromatographed eluting with hexane/ethyl acetate 8:2, to afford alcohol **4** (29.6 g, 98%); ^{1}H NMR: δ 7.29–7.00 (4H, m, aromatic hydrogens), 3.67 (2H, d, $J=6.9$, CH_2OH), 2.90 (2H, m, $(CH_3)_2CH$+CH_3CH), 1.26 (9H, m, $3CH_3$); GC/MS: $t_R=15.49$ min; m/z: 178 (M^+, 25), 147 (100), 105 (35).

4.3. (+)-2-(3-Isopropylphenyl)propan-1-ol (+)-4 and (−)-2-(3-isopropylphenyl)propan-1-ol acetate (−)-7

A mixture of **4** (25.0 g, 0.14 mol), *Porcine pancreatic* lipase (10.0 g), vinyl acetate (15 mL) in *t*-butyl methyl ether (150 mL) was stirred at room temperature for 96 h. The reaction mixture was filtered and concentrated under reduced pressure, to give a residue which was chromatographed eluting with hexane/ethyl acetate 9:1 The following products were recovered: (−)-**7** (12.1 g, 39%) e.e.=60% (chiral GC); (+)-**4** (9.22 g, 37%) e.e.=55% (chiral GC of the corresponding acetate). The enantiomeric excess of (−)-**7** was increased by hydrolysing (−)-**7** (KOH, MeOH), and submitting the corresponding alcohol to another enzymic reaction in the same conditions. After 48 h, (−)-**7** (3.83 g) was recovered with e.e. >99% (chiral GC): $[\alpha]_D^{20}=-10.8$ (*c* 1.09, $CHCl_3$); ^{1}H NMR: δ 7.39–7.00 (4H, m, aromatic hydrogens), 4.15 (2H, m, CH_2OAc), 3.07 (1H, m, CH_3CH), 2.89 (1H, m, $(CH_3)_2CH$), 2.03 (3H, s, CH_3COO), 1.30 (3H, d, $J=6.82$, CH_3CH), 1.25 (6H, d, $J=7.2$, $(CH_3)_2CH$); GC/MS: $t_R=18.10$ min; m/z: 220 (M^+, 1), 160 (100), 145 (92).

The e.e. of (+)-**4** was increased by repeating the enzymatic acetylation: after 120 h (+)-**4** (3.45 g) was recovered with e.e. >99% (chiral GC of the corresponding acetate); $[\alpha]_D^{20}=+10.8$ (*c* 1.54, $CHCl_3$); ^{1}H NMR and MS spectra were in accordance with those of the racemate.

4.4. (−)-2-(3-Isopropylphenyl)propan-1-ol (−)-4

Acetate (−)-7 (3.50 g, 0.016 mol) was hydrolysed with KOH (1.35 g, 0.024 mol) in MeOH (25 mL). After the usual work-up, (−)-4 (2.71 g, 95%) was recovered: $[\alpha]_D^{20}=-11.5$ (*c* 1.32, $CHCl_3$); ^{1}H NMR and MS spectra were in accordance with those of the racemate.

4.5. (+)-3-(3-Isopropylphenyl)butyronitrile (+)-8

To a solution of alcohol (−)-**4** (2.50 g, 0.014 mol) in pyridine (10 mL), 4-toluenesulphonyl chloride (3.46 g, 0.0182 mol) was added at 0°C. After the usual work-up, the residue was dissolved in DMSO (10 mL) and NaCN (0.823 g, 0.017 mol) was added. The mixture was heated at 50°C for 1 h, then diluted with water and extracted with methylene chloride. The organic phase was dried, and concentrated. The residue was purified by columnn chromatography, eluting with hexane/ethyl acetate 9:1, to afford (+)-**8** (1.62 g, 62%): $[\alpha]_D^{20}=+2.5$ (*c* 1.20, $CHCl_3$); ^{1}H NMR: δ 7.30–7.00 (4H, m, aromatic hydrogens), 3.15 (1H, m, CH_3CH), 2.90 (1H, m, $(CH_3)_2CH$), 2.58 (2H, m, CH_2CN), 1.45 (3H, d, $J=6.82$, CH_3CH), 1.25 (6H, d, $J=7.4$, $(CH_3)_2CH$); GC/MS: $t_R=17.83$ min; m/z: 187 (M^+, 31), 172 (46), 147 (100), 131 (69).

4.6. (−)-3-(3-Isopropylphenyl)butyronitrile (−)-8

According to the same procedure used for the conversion of (−)-**4** into (+)-**8**, from alcohol (+)-**4** (3.3 g, 0.018 mol) nitrile (−)-**8** (2.25 g, 65%) was prepared: $[\alpha]_D^{20}=-2.9$ (*c* 1.7, $CHCl_3$); ^{1}H NMR and MS spectra in accordance with those of the enantiomer.

4.7. (−)-3-(3-Isopropylphenyl)butanal (−)-1

To a solution of nitrile (+)-**8** (1.50 g, 8.02 mmol) in THF (15 mL) a solution of diisobutylaluminum hydride (1.5 M, 6.40 mL, 9.62 mmol) was added dropwise at −10°C. The reaction mixture was stirred at rt for 1 h, then poured into ice, quenched with a 5% solution of HCl, and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed eluting with hexane/ethyl acetate 9:1, to afford, after bulb-to-bulb distillation, enantiopure (−)-**1** (1.14 g, 75%); $[\alpha]_D^{20}=-27.8$ (*c* 1.37, $CHCl_3$); ^{1}H NMR: δ 9.71 (1H, t, $J=1.9$, *CHO*), 7.30–7.00 (4H, m, aromatic hydrogens), 3.35 (1H, m, CH_3CH), 2.90 (1H, m, $(CH_3)_2CH$), 2.75 (1H, ddd, $J=1.9$, 6.4, 16.4, C*H*CHO), 2.64 (1H, ddd, $J=1.9$, 7.9, 16.4, C*H*CHO), 1.32 (3H, d, $J=6.9$, CH_3CH), 1.25 (6H, d, $J=6.9$, $(CH_3)_2CH$); GC/MS: $t_R=16.26$ min; m/z: 190 (M^+, 32), 147 (100), 133 (16), 105 (68).

4.8. (+)-3-(3-Isopropylphenyl)butanal (+)-1

According to the same procedure described for (−)-**1**, (−)-**8** (2.20 g, 0.012 mol) was converted into (+)-**1** (1.64 g, 72%): $[\alpha]_D^{20}=+30.7$ (*c* 1.39, $CHCl_3$); ^{1}H NMR and MS spectra were in accordance with those of the opposite enantiomer.

4.9. 1-(3-Isopropenylphenyl)ethanone 10[13]

A solution of 1,3-diisopropenylbenzene (50.0 g, 0.32 mol) in CH_2Cl_2–MeOH (1:1 v/v, 600 mL) was treated with ozone at −78°C. The reaction mixture was quenched with triphenylphosphine, warmed to rt, and concentrated. The residue was chromatographed eluting with hexane/ethyl acetate 95:5, to afford derivative **10** (23.0 g, 45%); GC/MS: $t_R=15.04$ min; m/z: 160 (M^+, 5), 145 (100), 115 (46).

4.10. 1-(3-Isopropylphenyl)ethanone 11

Compound **10** (22.0 g, 0.137 mol) was hydrogenated in the presence of 5% Pd/C (2.0 g) in ethyl acetate solution (150 mL). After the usual work-up, the residue was chromatographed eluting with hexane/ethyl acetate 9:1, to afford compound **11** (21.8 g, 98%); ^{1}H NMR: δ 7.78 (2H, m, aromatic hydrogens), 7.43 (2H, m, aromatic hydrogens), 2.97 (1H, m, $(CH_3)_2CH$), 2.61 (3H, s, CH_3CO), 1.28 (6H, d, $J=6.8$, $(CH_3)_2CH$); GC/MS: $t_R=13.97$ min; m/z: 162 (M^+, 34), 147 (100).

4.11. 3-(3-Isopropylphenyl)but-2-enoic acid ethyl ester 12

A solution of compound **10** (21.0 g, 0.130 mol) and (triphenyl-λ^5-phosphanylidene)–acetic acid ethyl ester (68.4 g, 0.195 mol) in toluene (100 mL) was heated under reflux for 2 h. After the usual work-up, the residue was chromatographed eluting with hexane/ethyl acetate 8:2, to afford ester derivative **12** (17.8 g, 69%): (*E*)/(*Z*) = 10/1 (^{1}H NMR, $\delta_{CH=C}$ (*Z*)-**12** 5.93, d, J = 1.15 Hz); ^{1}H NMR major diastereoisomer: δ 7.45–7.00 (4H, m, aromatic hydrogens), 6.14 (1H, q, J = 1.15, *CH*=C), 4.22 (2H, q, J = 6.9, COO*CH*$_2$), 2.97 (1H, m, (CH$_3$)$_2$*CH*), 2.59 (3H, d, J = 1.15, *CH*$_3$C=), 1.32 (3H, t, J = 6.9, COOCH$_2$*CH*$_3$), 1.27 (6H, d, J = 6.6, (*CH*$_3$)$_2$CH); GC/MS: (i) (*E*)-**12** t_R = 21.88 min, m/z: 232 (M$^+$, 81), 217 (16), 187 (30), 171 (50), 144 (100); (ii) (*Z*)-**12** t_R = 19.96 min, m/z: 232 (M$^+$, 75), 217 (15), 187 (31), 171 (50), 144 (100).

4.12. 3-(3-Isopropylphenyl)but-2-enol 13

To a solution of **12** (17.0 g, 0.073 mol) in toluene (100 mL) a solution of Red-Al (3.5 M, 27.1 mL, 0.095 mol) was added dropwise at 0°C. The reaction mixture was stirred at rt for 2 h, poured into ice, quenched with a 5% HCl solution, and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), concentrated under reduced pressure. The residue was chromatographed eluting with hexane/ethyl acetate 8:2, to give derivative **13** (10.4 g, 75%): (*E*)/(*Z*) = 10/1 (^{1}H NMR, $\delta_{CH=C}$ (*Z*)-**13** = 5.69, tq, J = 7.1, 1.15 Hz); ^{1}H NMR major diastereoisomer: δ 7.45–7.00 (4H, m, aromatic hydrogens), 5.97 (1H, tq, J = 6.7, 1.15, *CH*=C), 4.35 (2H, d, J = 6.7, C*H*$_2$OH), 2.90 (1H, m, (CH$_3$)$_2$*CH*), 2.08 (3H, d, J = 1.15, *CH*$_3$C=), 1.26 (6H, d, J = 6.9, (*CH*$_3$)$_2$CH); GC/MS: (i) (*E*)-**13** t_R = 20.34 min, m/z: 190 (M$^+$, 38), 175 (15), 157 (7), 147 (100); (ii) (*Z*)-**13** t_R = 17.98 min, m/z: 190 (M$^+$, 23), 175 (9), 157 (4), 147 (100).

4.13. 3-(3-Isopropylphenyl)but-2-enal 9

A mixture of allylic alcohol **13** (10.0 g, 0.053 mol) and manganese(IV) oxide (1.5 equiv.) in methylene chloride (50 mL) was heated under reflux for 8 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was chromatographed eluting with hexane/ethyl acetate 8:2, to recover aldehyde **9** (8.91 g, 90%): (*E*)/(*Z*) 5:1 (^{1}H NMR, (*Z*)-**9** δ_{CHO} = 9.48, d, J = 8.1; $\delta_{CH=C}$ = 6.14, dq, J = 8.1, 1.15; $\delta_{MeC=C}$ = 2.32, d, J = 1.15). ^{1}H NMR major diastereoisomer: δ 10.19 (1H, d, J = 7.7, *CHO*), 7.45–7.00 (4H, m, aromatic hydrogens), 6.41 (1H, dq, J = 7.7, 1.15, *CH*=C), 2.95 (1H, m, (CH$_3$)$_2$*CH*), 2.58 (3H, d, J = 1.15, *CH*$_3$C=), 1.27 (6H, d, J = 6.9, (*CH*$_3$)$_2$CH); GC/MS: (i) (*E*)-**9** t_R = 20.11 min, m/z: 188 (M$^+$, 2), 187 (7), 173 (5), 145 (100); (ii) (*Z*)-**9** t_R = 18.48 min, m/z: 188 (M$^+$, 2), 187 (7), 173 (5), 145 (100).

4.14. (+)-3-(3-Isopropylphenyl)but-2-anol (+)-2

A suspension of baker's yeast (1.5 kg) and D-glucose (1.0 kg) in tap water (5.0 l) was stirred for 30 min at 32°C. The mixture was then treated with a solution of derivative **9** (9.0 g, 0.048 mol) in ethanol (10 mL). After 48 h at rt Celite (1 kg) was added, and the reaction mixture filtered, washing the Celite pad with ethyl acetate. The filtrate was adjusted to pH 4 with aqueous HCl (2N), and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed, eluting with hexane/ethyl acetate 8:2. An alcoholic fraction was recovered (5.52 g) with the following composition (GC/MS): **2** (49%), (*Z*)-**13** (21%), (*E*)-**13** (30%). To purify alcohol **2** from allylic alcohols, this fraction was dissolved in CH_2Cl_2 (30 mL) and treated with manganese(IV) oxide. The reaction mixture was heated under reflux for 8 h, filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed to remove the unsaturated aldehyde from the unreacted alcohol (+)-**2**. Derivative (+)-**2** was thus recovered in pure form (1.95 g, 21%): $[\alpha]_D^{20}$ = +16.6 (*c* 1.25, $CHCl_3$); e.e. = 97% (chiral HPLC); ^{1}H NMR: δ 7.30–7.00 (4H, m, aromatic hydrogens), 3.57 (2H, m, *CH*$_2$OH), 2.87 (2H, m, (CH$_3$)$_2$*CH*+CH$_3$*CH*), 1.85 (2H, q, J = 6.5, C*H*$_2$CH$_2$OH), 1.27 (3H, d, J = 6.9, *CH*$_3$CH), 1.25 (6H, d, J = 7.0, (*CH*$_3$)$_2$CH); GC/MS: t_R = 17.63 min; m/z: 192 (M$^+$, 54), 174 (4), 147 (92), 131 (63), 105 (100).

4.15. (+)-3-(3-Isopropylphenyl)but-2-anal (+)-1

A solution of derivative (+)-**2** (1.80 g, 9.4 mmol) in CH_2Cl_2 (5 mL) was added to a solution of pyridinium chlorochromate (4.31 g, 0.020 mol) in CH_2Cl_2 (10 mL). The reaction was stirred at rt for 2 h. After the standard work up, the residue was chromatographed eluting with hexane/ethyl acetate 9:1, to afford, after bulb-to-bulb distillation, derivative (+)-**1** (1.09 g, 61%) in pure form: $[\alpha]_D^{20}$ = +27.9 (*c* 1.26, $CHCl_3$).

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