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Bio-catalysed synthesis of optically active Undecavertol® enantiomers

Agnese Abate, Elisabetta Brenna* and Ginevra Fregosi

Dipartimento di Chimica, Materiali ed Ingegneria Chimica del Politecnico, Via Mancinelli 7, I-20131 Milano, Italy

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Abstract—Two enantiomers of Undecavertol® were prepared by enzymatic methods and their odour properties evaluated.

1. Introduction

Fragrance materials are employed in a wide range of products ranging from perfumes to skin products such as creams, lotions, detergents and several other personal and household products. Allergic skin reactions to fragrances have been observed in the past by some users, but recently this problem has become very topical and the real size of the problem has yet to be established. The European Commission's Scientific Committee on Cosmetics and other Non-Food Products (SCCNFP) recognised that some perfume constituents elicit dermatological reactions. This committee listed 26 substances as skin-sensitising ingredients.[1] According to the proposed Seventh Amendment of the European Cosmetic Directive, which has become effective on March 11, 2005, the identity of these compounds in cosmetics should be labelled if they exceed 10 ppm in products intended to remain on the skin, or 100 ppm in products intended to be rinsed off therefrom. Among these 26 allergens, there are very common natural compounds, such as citronellol, limonene, eugenol and cinnamic aldehyde.

In light of these observations, the investigation of the properties of the single enantiomers of chiral odourants is now of primary importance for three main reasons. First of all, as the enantiomers of chiral drugs may have different pharmacological activities and side effects, the enantiomers of chiral fragrances may show different interactions with human beings, not only from an odour perception point of view.[2] Second, it is necessary to find new odourants to replace the 26 allergenic fragrances. New odour sensations can be developed by preparing new synthetic odourous molecules or investigating the odour response of enantiomers. Finally, if two enantiomers show very different odour thresholds, the most potent one can be employed in commercial formulations in a reduced amount, thus decreasing the quantity of chemicals interacting with human beings.

The preparation of enantiomerically pure stereoisomers of chiral odourants is a relevant research topic. We have shown over the last few years that this goal can be satisfactorily reached by using enzyme-mediated approaches, that is, lipase-catalysed kinetic resolutions and stereoselective bakers' yeast reactions.[3] Herein, we report on the preparation of the two enantiomers of the commercial odourant Undecavertol® **1** (Givaudan) by means of lipase-mediated acetylation.

2. Results and discussion

On the website of Givaudan,[4] Undecavertol® is described to have a powerful green-floral character, somewhat related to lily-of-the-valley, with natural fresh fruity violet leaf and linden blossom aspects. It can be used successfully in rose and fruity-pear accords. It requires careful dosage and blending due to its exceptional strength. Undecavertol® is also widely employed both in fine and functional perfumery. The commercial product is a 98.5:1.5 mixture (GC/MS) of *trans*- and *cis*-isomers.

Aldolic condensation of propanal, to give (*E*)-2-methyl-2-pentenal, followed by Grignard addition of pentyl

* Corresponding author. Tel.: +39 02 23993077; fax: +39 02 23993080; e-mail: elisabetta.brenna@polimi.it

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magnesium bromide[5] allowed us to prepare racemic **1**, as a 97.3:2.6 mixture (GC/MS) of *trans*- and *cis*-isomers. Lipase-mediated acetylation of racemic **1** was investigated in the presence of three commercial enzymic preparations (lipase PS, PPL, CCL) in *t*-butyl methyl ether solution, using vinyl acetate as an acyl donor. In all cases, the reaction was rather slow with the highest value of enantioselectivity being observed with lipase PS (see Table 1). Lipase PS-mediated acetylation of (±)-**1** (6 days) gave acetate derivative (+)-**2** as a 93.5:6.5 mixture of *trans*- and *cis*-isomers (GC/MS) (Scheme 1). This latter was hydrolysed by reaction with KOH in methanol, with the corresponding alcohol (+)-**1** being obtained as a 96.5:3.5 mixture of *trans*- and *cis*-isomers (GC/MS). The enantiomeric excess was evaluated to be 93% by using lanthanide chiral shift reagents.

Table 1.

Enzyme	ee (%) of (*R*)-**2**	ee (%) of (*S*)-**1**
Lipase PS	93	75
CCL	35	Racemic
PPL	37	Racemic

The unreacted alcohol was treated with lipase PS, in *t*-butyl methyl ether solution, in the presence of vinyl acetate for 10 days. At the end of this period, (−)-**1** was recovered from the reaction mixture by column chromatography. Compound (−)-**1** was found to contain 2% of the *cis*-isomer by GC/MS. The enantiomeric excess was evaluated to be 75% by using lanthanide chiral shift reagents.

The absolute configuration was assigned by converting (−)-**1** into (*S*)-(+)-**3**[6] by ozonolysis followed by triphenylphosphine quenching. The samples of (+)-**1** (ee = 93%) and (−)-**1** (ee = 75%) were evaluated by Givaudan perfumers and the following results were obtained.

Compound (*R*)-(+)-**1**: Typical Undecavertol® odour, floral, green, fresh, violet leaves, stronger and greener than the racemic commercial material, with aspects of cucumber and Neofolione (methyl non-2-enoate). Odour threshold: 0.31 ng/L air.

Compound (*S*)-(−)-**1**: Weaker enantiomer, fruity-green pinefir balsam note with aspects of tea, not so typical of Undecavertol®. Odour threshold: 4.7 ng/L air.

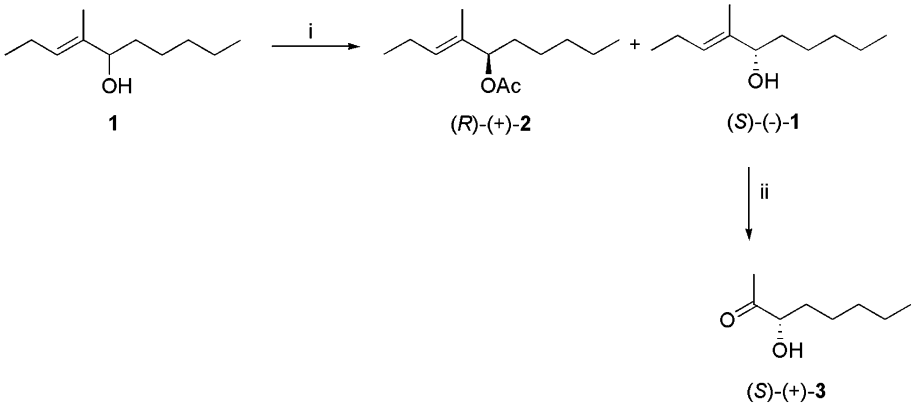
3. Conclusion

The two Undecavertol® enantiomers were found to show different odour qualities and strengths. Compound (*R*)-(+)-**1** was the most potent, and showed the best odour profile. It can be used in perfume compositions in half dosage with respect to the racemate. In this way the same odour sensation can be elicited by employing a minor quantity of chemicals in products that are directly in contact with human body.

The use of enzyme-mediated approach allowed once again to obtain rapidly both the enantiomers of the secondary allylic alcohol **1**.

4. Experimental

Lipase PS *Burkholderia cepacia* (Amano Pharmaceuticals Co., Japan), *Porcine pancreatic* lipase (PPL type II, Sigma), *Candida rugosa* lipase (CRL, Sigma) were employed in this work. GC–MS analyses were performed on a HP 6890 gas-chromatography equipped with a 5973 mass detector, using a HP-5MS column (30 m × 0.25 mm × 0.25 μm). The following temperature programme 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 on a Bruker AC-250 spectrometer (250 MHz ^{1}H). 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 chromatographic separations were carried out on silica gel columns. Chiral shift reagent NMR experiments were



Scheme 1. Reagents and conditions: (i) Lipase PS, vinyl acetate, *t*-butylmethyl ether; column chromatography; (ii) O_3, CH_2Cl_2/MeOH, −78 °C; then PPh_3.

performed on a Bruker 400, by using Eu(hfc)$_3$ and monitoring the signal of the methyl group linked to the double bond [2.75 ppm for (*S*)-**1** and 2.81 ppm for (*R*)-**1**].

4.1. (*E*)-2-Methyl-2-pentenal

Propanal (58 g, 1.0 mol) was added dropwise over 30 min to a solution of sodium hydroxide 1 M (40 mL). The reaction mixture was stirred at room temperature for 1 h, and then poured into water, extracted with diethyl ether, dried and concentrated. The crude product was purified by distillation under reduced pressure (bp 80–81 °C/100 mmHg), to give the title product (75.4 g, 77%). Chemical purity 90% by GC/MS; t_R = 3.25 min; *m*/*z*: 98 (M^+, 100), 83 (33), 69 (55), 55 (48), 41 (100). ^{1}H NMR ($CDCl_3$): δ 9.38 (s, 1H, C*H*O), 6.47 (t, *J* = 7.3 Hz, 1H, *H*–C=C), 2.35 (m, 2H, CH_2C=), 1.71 (s, 3H, CH_3C=), 1.09 (t, *J* = 7.5 Hz, 3H, CH_3CH_2).

4.2. (*E*)-4-Methyl-3-decen-5-ol 1

(*E*)-2-Methyl-2-pentenal (73.0 g, 0.745 mol) was added dropwise to a solution of pentyl magnesium bromide (prepared from 1.102 mol of pentyl bromide and 2.136 mol of magnesium in 800 mL of diethyl ether) at 10 °C. The mixture was refluxed for 1 h, poured into ice, quenched with satd NH_4Cl solution, and extracted with diethyl ether. The organic phase was dried, concentrated and purified by column chromatography (86.1 g, 68%). Chemical purity 96% by GC/MS; t_R = 12.05 min; *m*/*z*: 170 (M^+, 6), 152 (10), 141 (50), 99 (100). ^{1}H NMR ($CDCl_3$): δ 5.34 (t, *J* = 7.0 Hz, 1H, *H*–C=C), 3.95 (t, *J* = 6.7 Hz, 1H, C*H*OH), 2.01 (m, 2H, CH_2C=), 1.57 (s, 3H, CH_3C=), 1.55–1.10 (m, 8H, 4CH_2), 0.94 (t, *J* = 7.3 Hz, 3H, CH_3CH_2C=), 0.86 (t, *J* = 6.6 Hz, 3H, CH_3).

4.3. (5*R*,3*E*)-4-Methyl-3-decen-5-yl acetate and (5*S*,3*E*)-4-methyl-3-decen-5-ol

A mixture of racemic **1** (25 g, 0.147 mol), lipase PS (5 g) and vinyl acetate (15 mL) in *t*-butylmethyl ether (200 mL) was stirred at rt for 6 days. The residue obtained upon evaporation of the filtered mixture was chromatographed. Column chromatography (hexane–AcOEt 95:5) allowed us to recover the acetyl derivative (*R*)-(+)-**2** (7.2 g, 23%) and unreacted alcohol **1** (16.2 g, 65%).

Data of (*R*)-(+)-**2**: chemical purity = 97% (GC/MS), de = 87% (GC/MS), t_R = 14.14 min; *m*/*z*: 197 (M^+−15, 1), 170 (65), 152 (50), 99 (100); ee (by chiral shift reagent experiments on the corresponding alcohol) = 93%; $[\alpha]_D^{20}$ = +29.6 (*c* 1.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 5.42 (t, *J* = 7.0 Hz, 1H, *H*–C=C), 5.10 (t, *J* = 6.9 Hz, 1H, C*H*OAc), 2.04 (s + m, 5H, OAc + CH_2C=C), 1.60 (s, 3H, CH_3C=C), 1.60–1.10 (m, 8H, 4CH_2), 0.94 (t, *J* = 7.3 Hz, 3H, CH_3CH_2C=), 0.88 (3H, t, *J* = 6.6 Hz, CH_3).

Unreacted alcohol **1** (16.0 g, 0.094 mol) was treated again with lipase PS, in the same conditions, to afford, after 10 days, enantiomerically enriched (*S*)-(−)-**1** (9.9 g, 62%): chemical purity = 93% (GC/MS), de = 96% (GC/MS), ee (by chiral shift reagent experiments on the corresponding alcohol) = 75%, $[\alpha]_D^{20}$ = −4.9 (*c* 0.98, $CHCl_3$). MS and NMR data in accordance with those of the racemate.

4.4. (3*E*,5*R*)-4-Methyl-3-decen-5-ol

Saponification of (*R*)-(+)-**2** (7.0 g, 0.033 mol) with KOH (2.21 g, 0.039 mol) in MeOH (50 mL) at rt gave (*R*)-(+)-**1** (4.99 g, 89%): chemical purity 98% (GC/MS), de = 87% (GC/MS), ee = 93% (chiral shift reagents); $[\alpha]_D^{20}$ = +6.5 (*c* 1.16, $CHCl_3$). MS and NMR data in accordance with those of the racemate.

4.5. Determination of the absolute configuration of (−)-1

A solution of (−)-**1** (0.500 g, 0.0031 mol) in CH_2Cl_2–MeOH 7:3 (50 mL) was treated with ozone at −78 °C. After 10 min the mixture was quenched with triphenylphosphine, warmed at rt, poured into water, extracted with CH_2Cl_2, dried and concentrated. The residue was chromatographed eluting with hexane–AcOEt 95:5, to give (*S*)-(+)-**3** (0.299 g, 67%): chemical purity 98% (GC/MS), t_R = 8.10 min; *m*/*z*: 144 (M^+, 1), 126 (1), 111 (1), 101 (45), 83 (90), 55 (100). ^{1}H NMR in accordance with that described in the literature.[6] $[\alpha]_D^{20}$ = +57.3 (*c* 1.1, $CHCl_3$) {lit.[6] for (*S*)-**3** $[\alpha]_D^{20}$ = +92 (*c* 0.03, $CHCl_3$)}.

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