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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 3073–3077

Stereochemical aspects of the bioreduction of the conjugated double bond of perillaldehyde

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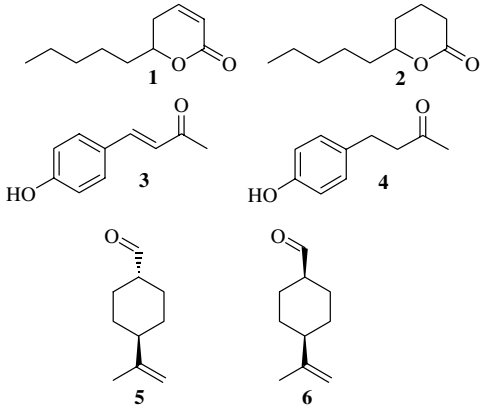
Received 16 June 2004; accepted 23 August 2004

Abstract—A study on the regioselective reduction of the conjugate double bond of perillaldehyde is described. The chemical reduction of this substrate was investigated in order to provide a straightforward access to the relevant natural flavour, dihydroperillaldehyde. The biological reduction of both natural (*S*)-(−)-perillaldehyde and synthetic (*R*)-(+)-perillaldehyde was accomplished by means of fermenting baker's yeast. The latter microorganism converted, with different diastereoselectivity, the (*S*)- and (*R*)-enantiomers into the corresponding *trans* and *cis* saturated alcohols, respectively. The origin of the hydrogen atoms added to the double bond was studied by deuterium labelling experiments and ^{2}H NMR measurements that clearly demonstrate a different mechanism of the biohydrogenation of the two enantiomeric forms of perillaldehyde.

1. Introduction

The sensorial properties of many α,β-unsaturated natural flavours are frequently very different in comparison with those showed by their corresponding saturated analogues. Although the hydrogenation process is often straightforward, recent legislation[1] has meant that flavour substances labelled 'natural' may only be prepared either by physical processes (extraction from natural sources) or by enzymatic/microbial processes, which involve precursors isolated from nature. Since consumers prefer natural food components, a number of studies devoted to their biogeneration from easily available extractive materials have been developed in the past years. These latter preparations are especially relevant when the flavour substances are present in nature in trace amounts and are not accessible by extraction.

In this context, we have studied different methods of biohydrogenation of the activated double bonds of some natural products. Several relevant examples are the couples (*R*)-2-decen-5-olide **1** (Massoia lactone)/δ-decanolide **2**[2] and 4-(4-hydroxyphenyl)-2-but-3-en-2-one **3**/4-(4-hydroxyphenyl)-2-butanone (raspberry ketone) **4**[3] (Scheme 1) where both the use of different microorganisms and the stereochemical outcome of the reduction were investigated extensively.



Scheme 1.

Recently, 1,2-dihydroperillaldehyde (compounds **5** and **6**) was reported for the first time as a natural product.[4] The mixture of the *trans*- and *cis*-isomers was found in the essential oil of *Enhydra fluctuans*. The latter plant is a species common in south Asia, where it is used in folk medicine and as a condiment in food.

We prepared some samples of synthetic dihydroperillaldehydes that were submitted to sensorial evaluation

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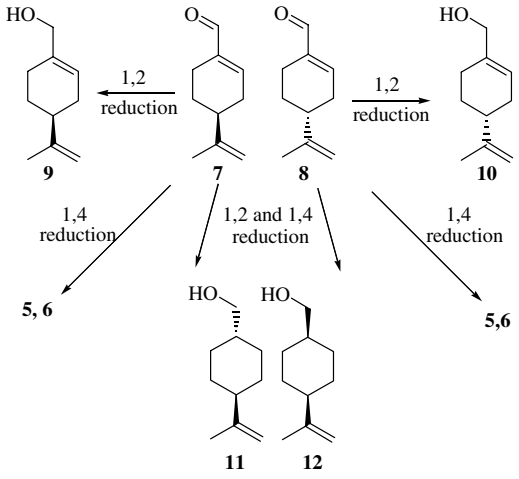
doi:10.1016/j.tetasy.2004.08.025

performed by experienced perfumers. Surprisingly, it was observed that the latter compound is suitable at a dilution level of 0.2 ppm in order to impart an effective watery character to fruit formulations. The best application seems to be its use in watermelon aroma since the main part of the flavour sold on the marked is lacking this feature and shows an undesirable melon side note.

These observations prompted us to study the bioreduction of the natural and easy available (*S*)-(−) perillaldehyde **7** to obtain the corresponding C1 saturated analogues **5**, **6**, **11** and **12** (Scheme 2). The key step of the process is the hydrogenation of the conjugated double bond. Otherwise the oxidation/reduction of the alcoholic functionality could be performed by a number of biological procedures.[5] We selected baker's yeast as the 'natural' reducing agent for this kind of transformation since it proved to be a versatile tool in the selective reduction of many α,β-unsaturated aldehydes, ketones and lactones.[6]



Scheme 2. Reduction of the α,β-unsaturated aldehydes **7** and **8**.

Herein we report on the study of the baker's yeast mediated reduction of the C1 double bond of natural and artificial perillaldehyde (*S*)-(−)-**7** and (*R*)-(+)-**8**, respectively. The stereochemistry of the process was investigated by deuterium labelling experiments and by ^{2}H NMR studies.

2. Results and discussion

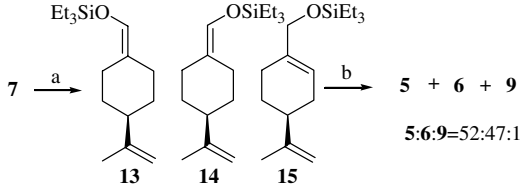
2.1. Chemical reduction of natural perillaldehyde

First we needed a significant amount of dihydroperillaldehyde in order to perform its olfactory evaluation. Therefore, we explored its preparation by chemical reduction of the easy available (−)-perillaldehyde **7**. Since the latter compound shows two double bonds and one stereogenic centre, this preparation involves some problems of regio and diastereoselectivity. In fact, only the conjugated double bond should be reduced and a mixture of *trans*/*cis*-isomers should also be possible.

Few examples of this regioselective process have been described in the literature. Murphy and Prager[7] reported a procedure where perillaldehyde dissolved in a mixture of ether, anhydrous ammonia and propan-2-ol was treated with lithium wire. The reaction afforded a 3:1 mixture of *cis*/*trans*-isomers of the dihydro derivative even if on a large scale, complete reduction to *p*-menthan-7-ol occurred.

Subsequently, Brestensky and Stryker[8] described the regioselective conjugate reduction of perillaldehyde by the use of the copper (I) hydride complex $[(Ph_3P)CuH]_6$ in the presence of Me_3SiCl. This procedure provided the saturated silyl enol ether, which was then hydrolysed to give a 2:1 mixture of dihydroperillaldehyde isomers. Furthermore, the C1 double bond of perillaldehyde[9] or perillyl alcohol **9**[10] was reduced by sodium metal but the products in both cases were the saturated alcohols **11** and **12**.

A further oxidative step to dihydroperillaldehyde was hence necessary. Therefore, we studied a straightforward method of reduction that could be applicable on a large-scale transformation and did not involve the use of an expensive reducing agent. We found that the above mentioned selective hydrogenation can be easily achieved by a one-pot procedure based on the use of a rhodium (I) complex catalysed hydrosilylation reaction.[11] In effect, the treatment of perillaldehyde with triethylsilane in the presence of a catalytic amount of $(Ph_3P)_3RhCl$ (0.3 mol%) gave the corresponding saturated silyl enol ethers **13** and **14** in good yields as a 1:1 mixture of isomers[†] (Scheme 3).



Scheme 3. Chemical reduction of (*S*)-(−)-perillaldehyde: (a) Et_3SiH, $(Ph_3P)_3RhCl$ cat, THF; (b) H_2O/THF, 5% HCl aq soln; 68% overall.

The only side product of the reaction was a trace amount of **15** deriving from a 1,2-reduction, whereas the starting material was consumed completely. The following acidic hydrolysis afforded a 1:1 mixture of *trans*-**5** and *cis*-**6** dihydroperillaldehyde that were separated from the silanol by chromatography and/or distillation.

2.2. Baker's yeast mediated reduction of natural perillaldehyde

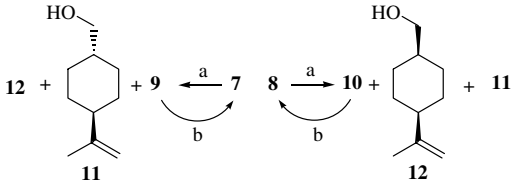
With an effective synthetic method to dihydroperillaldehyde in hand, the next step was looking for an analogous transformation by means of biological reduction. To the best of our knowledge, only one paper dealing

[†] Compounds **13**, **14** and **15** were not isolated. The GC–MS analysis of the reaction mixture revealed two peaks (**13** and **14**; t_R: 21.10; and 21.38; ratio 51:48% of total) showing M^+ 266. A further peak (t_R: 21.26; ratio 1% of total) showed M^+ 266 and was conceivably due to compound **15**.

with microbiological transformation of perillaldehyde is reported in the literature. This work[12] describes a study on the biotransformation of different monoterpenoids by *Euglena gracilis Z*. The latter photosynthetic microorganism converts perillaldehyde **7** into a mixture of perillic alcohol **9**, dihydroperillic alcohol **11**, 1,2-dihydroperillic acid and 8,9-dihydroperillic acid. Furthermore, the incubation of perillaldehyde **8** gives a similar product distribution. These results also show that the isolated double bond is reduced and an undesirable over-oxidation of the aldehydic functionality occurs as a side reaction of the process.

As mentioned above, we selected baker's yeast as the microorganism of choice for the reduction of α,β-unsaturated aldehydes. It is known that fermenting baker's yeast stereoselectively reduces the conjugated double bond of carbonyl compounds with an efficiency and stereoselectivity dependent on the structural features of the substrates. We have previously applied this approach in the enantioselective reduction of prochiral aldehydes[13] and accordingly, extended this acquired biotechnological methodology to the reduction of perillaldehyde.

In order to achieve a large-scale preparation of the reduction products, we performed the microbial reduction by adsorbing the substrates on a non-polar resin (XAD 1180). This procedure allowed us to use a high concentration of substrate (8–15 g/L) and the products were recovered by simple filtration of the resin. Extraction of the latter with a suitable solvent gave the crude reaction mixture. We found that incubation of fermenting baker's yeast with (*S*)-(−)-perillaldehyde afforded, almost exclusively, a mixture of perilyl alcohol **9** (51%) and saturated compounds **11** and **12** (48%) in an 89:11 ratio, respectively (Scheme 4).



Scheme 4. Baker's yeast reduction of perillaldehyde: (a) baker's yeast, glucose, water, 4 days; (b) MnO_2, $CHCl_3$ reflux, 5 h.

Only traces of the starting aldehyde (<1%) were detected at the end of reaction (4 days). The crude mixture was easily purified by treatment with MnO_2 in refluxing $CHCl_3$ to afford (*S*)-(−)-perillaldehyde **7** and alcohols **11** and **12** that were separated by chromatography.

Otherwise, a similar procedure performed on (*R*)-(+)-perillaldehyde **8** showed similar results in terms of effectiveness but very different results with respect to diastereoselectivity. In fact, the ratio of allylic alcohol/saturated alcohols was the same but the *trans*/*cis* ratio of the products deriving from double bond reduction was reversed. In this case *cis*-alcohol **12** was the major diastereoisomer with a *cis*/*trans* ratio of 80:20.

2.3. Stereochemistry of the baker's yeast mediated double bond saturation

In order to explain the observed behaviour of this diastereoselective reduction, we investigated the origin of the hydrogen atoms formally added to the conjugate double bond. To this end, the yeast transformations were performed in the presence of deuterated water according to the procedure described above.

Previous works[2,3a,14] carried out on the baker's yeast reduction of α,β-unsaturated carbonyl derivatives showed that the addition of hydrogen to the double bond may occur with different stereochemistry. The global mechanism of the addition suggests that the hydrogen at the β-position originates from the NADPH enzyme while that at the α-position is picked up from the medium; the resulting stereochemistry of the reduction may be *anti* or *syn* depending on the substrate. Accordingly, in our case the labelling experiments showed that the incorporation occurred at positions 1, 2 and 7 (*p*-menthane numbering).

The deuterium at position 1 originates from the solvent while the deuterium atoms at position 2 and 7 are incorporated as hydrides in the reduction step from the reduced form of the nicotinamide cofactor, which exchanges the deuterium atoms with the solvent under the action of a diaphorase.[15] The ^2H NMR spectra (Fig. 1) of the mixtures **11**/**12** obtained from **7** and **8** are reported in Figure 1 and allow some interesting considerations.

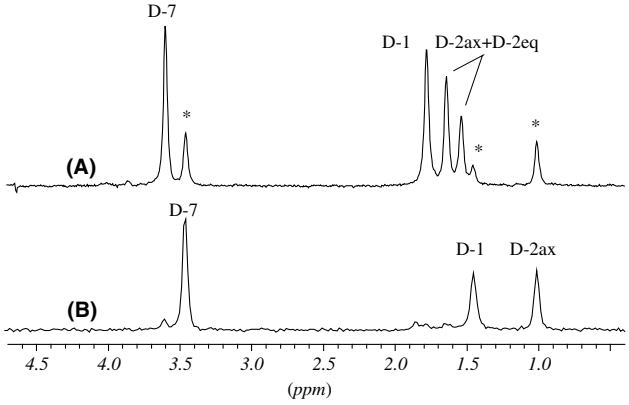
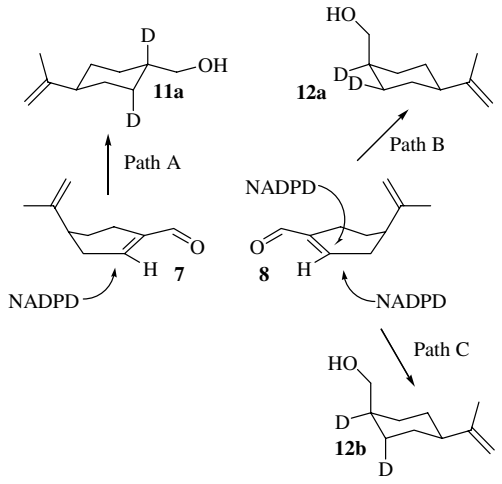


Figure 1. ^2H NMR spectra in $CHCl_3$ of (A) mixture of compounds **12** and **11** obtained by baker's yeast reduction of (*R*)-(+)-perillaldehyde (asterisks denote signals belonging to the minor *trans*-isomer **11** and (B) mixture of compounds **11** and **12** obtained by baker's yeast reduction of (*S*)-(−)-perillaldehyde (only traces of the *cis*-isomer **12** appear in the spectrum).

Compound **11a** (Scheme 5) showed that the deuterium atoms at positions 1 and 2 at 1.01 and 1.46 ppm, respectively, are axially oriented as deduced from the large coupling constant of 12.5 Hz occurring between the corresponding hydrogen nuclei in the proton spectrum. Thus, they conceivably derive from a *trans* addition of deuterium to the double bond, where the NADPD undertook delivery of hydride on the *Re* face of **7**



Scheme 5. Proposed mode of labelling of **11** and **12**.

(path A). Otherwise, compound **12** was formed as a mixture of **12a** and **12b** both deriving from **8** by a *trans* addition to the *Re* face (path B) and *syn* addition to the *Si* face (path C).

3. Conclusion

These results, seen together, can be explained in terms of the different enantioselectivities of the reducing enzymes. It is reasonable to assume that (*S*)-perillaldehyde was transformed through a *trans* addition, in accordance with the behaviour of the enoyl-CoA mediated reduction. Otherwise, (*R*)-perillaldehyde was not a good substrate for the latter enzyme and the biotransformation proceeded with loss of stereocontrol, due probably to a concomitant operation of different reducing enzymes.

4. Experimental

4.1. General experimental

TLC: Merck silica gel 60 F_{254} plates. Column chromatography (CC): silica gel. GC: HP-6890 gas chromatograph; diastereoisomer excesses determined on a HP-5 column (30 m × 0.32 mm; Hewlett Packard) with the following temp. program 60° (1 min)–6°/min–150° (1 min)–12°/min–280° (5 min); t_R given in min. ^{1}H and ^{13}C spectra: $CDCl_3$ solns at rt; Bruker-ARX 400 spectrometer at 400 MHz; ^{2}H spectra: $CHCl_3$ solns at rt; Bruker-ARX 400 spectrometer at 61.4 MHz. The ^{2}H spectra were acquired with broad band ^{1}H decoupling to suppress the heteronuclear proton/deuterium coupling constants to improve the signal resolution. The chemical shifts in ppm are relative to internal $SiMe_4$ (= 0 ppm), *J* values in Hz. Mass spectra were measured on a Finnigan-Mat TSQ 70 spectrometer; *m/z* (rel.%). IR spectra were recorded on a Perkin–Elmer 2000 FT-IR spectrometer; films. Microanalyses were determined on an analyser 1106 from Carlo Erba.

Baker's yeast was obtained from Gist-brocades (DSM Bakery Ingredients Italy spa). Natural (*S*)-(−)-perillaldehyde of undefined origin was commercially available from Aldrich; (*R*)-(+)-perillaldehyde was prepared by MnO_2 oxidation of (*R*)-(+)-perillyl alcohol (Fluka).

4.2. Chemical reduction of (*S*)-(−)-perillaldehyde

A solution of (*S*)-(−)-perillaldehyde (25 g, 167 mmol) in dry THF (25 cm^3) was treated under nitrogen with Et_3SiH (28.7 cm^3, 180 mmol) and $(Ph_3P)_3RhCl$ (0.5 g, 0.54 mmol). The mixture was stirred and heated at 50 °C for 3 h. After cooling to rt, the reaction was diluted with THF (100 cm^3), water (30 cm^3) and 5% HCl aq (10 cm^3). The stirring was prolonged for a further 2 h and then the mixture diluted with water (500 cm^3) and extracted with ether (3 × 150 cm^3). The combined organic phases were washed with brine (100 cm^3), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (hexane → hexane/ethyl acetate 9:1) and bulb to bulb distillation (bp 90–95 °C/20 Torr) to afford pure dihydroperillaldehyde (17.2 g, 68%) as a 1:1 mixture of *trans*/*cis*-isomers **5** and **6**, respectively. FT-IR (film) 3085, 2709, 1730, 1645, 1451, 1375, 963, 923, 888, 812; *m/z* (EI) *trans*-isomer (t_R 10.58): 152 (M^+, 55), 137 (10), 134 (16), 121 (86), 119 (63), 109 (76), 105 (28), 95 (56), 93 (45), 91 (50), 81 (100), 79 (79), 77 (30), 67 (93), 55 (49); *cis*-isomer (t_R 10.50): 152 (M^+, 23), 137 (5), 134 (12), 121 (29), 119 (21), 109 (42), 105 (12), 95 (28), 93 (25), 91 (22), 81 (100), 79 (48), 77 (15), 67 (68), 55 (36); δ 1.12–1.42 (6H, m), 1.52–1.73 (4H, m), 1.66 (3H, s, CH_3), 1.72 (3H, s, CH_3), 2.00–1.79 (4H, m), 2.18–2.00 (2H, m), 2.32-2.18 (3H, m), 2.45 (1H, m, H-1), 4.62 (1H, br s, C=C*H*H), 4.67 (1H, br s, C=C*H*H), 4.69 (2H, br s, C=CH_2), 9.63 (1H, s, C*H*O), 9.72 (1H, s, C*H*O). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.80; H, 10.60.

4.3. Baker's yeast mediated reduction of perillaldehyde

4.3.1. Reduction of natural (*S*)-(−)-perillaldehyde. A 5 L open cylindrical glass vessel equipped with a mechanical stirrer was charged with tap water (2 L) and glucose (150 g). Fresh baker's yeast (500 g) was added in small pieces to the stirred mixture and the fermentation allowed to proceed for 2 h. Aldehyde **7** (20 g, 133 mmol), absorbed on the resin XAD 1180 (100 g), was added in one portion. Vigorous stirring was continued for 4 days at room temperature. During this time, more baker's yeast (100 g) and glucose (50 g) were added after 24 and 48 h after the fermentation had started. The resin was then separated by filtration on a sintered glass funnel (porosity 0, >160 μm) and the water phase extracted again with further resin (50 g). The combined resin crops were extracted with ethyl acetate (4 × 100 cm^3) and the acetate solution washed with brine. The dried organic phase (Na_2SO_4) was concentrated under reduced pressure to give an oil (25 g). The latter was dissolved in $CHCl_3$ and treated with MnO_2 (40 g, 460 mmol) with stirring at reflux for 5 h. The residue obtained upon filtration and evaporation of the $CHCl_3$ phase was purified by column chromatography using

hexane–ethyl acetate (9:1–3:1) as the eluent to give a mixture of **11** and **12** (9.9 g, 48%) as a pale yellow oil. The diastereomeric ratio was 91:9 (determined by NMR analysis). FT-IR (film) 3338, 1644, 1449, 1375, 1093, 1035, 970, 886; *m*/*z* (EI) *trans*-isomer (t_R 12.10): 154 (M^+, 26), 136 (28), 121 (91), 108 (48), 107 (74), 93 (100), 81 (50), 79 (85), 67 (61), 55 (29), 41 (30); ^{1}H NMR of **11** δ 1.01 (2H, qd, *J* ca. 12.5 and 3.6, H-2_{ax}, 6_{ax}), 1.46 (1H, m, H-1), 1.71 (3H, t, *J* 1.2, CH_3), 1.86 (1H, m, H-2_{eq}, 6_{eq}), 1.22 (2H, qd, *J* ca. 13 and 3.6, H-3_{ax}, 5_{ax}), 1.82 (1H, m, H-3_{eq}, 5_{eq}), 1.47 (1H, m, H-4), 3.47 (2H, d, *J* 6.2, CH_2OH), 4.67 (2H, m, =CH_2). The spectral assignment is based on the values of vicinal coupling constants and the chemical shift correlation experiments (COSY). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.90; H, 11.70.

4.3.2. Reduction of synthetic (*R*)-(+)-perillaldehyde. The same procedure described above was performed on (*R*)-(+)-perillaldehyde **8** (10 g, 67 mmol) to give an 80:20 mixture of *cis*/*trans*-isomers **12** and **11** (4.2 g, 40%). FT-IR (film) 3335, 1645, 1450, 1373, 1093, 1053, 1032, 951, 886; *m*/*z* (EI) *cis*-isomer **12** (t_R 12.40): 154 (M^+, 13), 136 (32), 121 (65), 108 (41), 107 (84), 93 (100), 81 (61), 79 (96), 67 (70), 55 (34), 41 (34); ^{1}H NMR of **12** δ 1.53 and 1.62 (4H, m, H-2_{ax}, 6_{ax} and H-2_{eq}, 6_{eq}, not assigned), 1.47 and 1.54 (4H, m, H-3_{ax}, 5_{ax} and H-5_{eq}, 5_{eq}, not assigned), 1.74 (3H, t, *J* 1.2 Hz, CH_3), 1.99 (1H, m, H-4), 3.60 (2H, d, *J* 7.3 Hz, CH_2OH), 4.72 (2H, m, =CH_2). The spectrum was very crowded and could not be completely analysed. The assignment above is based on the chemical shift correlation experiments (COSY) and selective total correlation spectroscopy (TOCSY-1D). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.00; H, 11.65.

4.4. Baker's yeast mediated reduction of perillaldehyde in D_2O and ^{2}H NMR measurements

4.4.1. Reduction of natural (*S*)-(−)-perillaldehyde. A 1 L open cylindrical glass vessel equipped with a mechanical stirrer was charged with tap water (500 cm^3) D_2O (100 cm^3) and glucose (50 g). Fresh baker's yeast (250 g) was added in small pieces to the stirred mixture and the fermentation allowed to proceed for 2 h. Aldehyde **7** (12 g, 80 mmol), absorbed on the resin XAD 1180 (50 g), was added in one portion. Vigorous stirring was continued for 4 days at room temperature. During this time more baker's yeast (50 g) and glucose (50 g) were added after 48 h since the fermentation started. The resin was then separated by filtration on a sintered glass funnel (porosity 0, >160 μm) and the water phase extracted again with further resin (40 g). The combined resin crops were extracted with ethyl acetate (4×60 cm^3) and the acetate solution washed with brine. The dried organic phase (Na_2SO_4) was concentrated under reduced pressure to give an oil (13 g). The latter was dissolved in $CHCl_3$ and treated with MnO_2 (40 g) stirring at reflux for 5 h. The residue obtained upon filtration and evaporation of the $CHCl_3$ phase was purified by column chromatography using hexane–ethyl acetate (9:1–3:1) as the eluent to give a mixture of **11** and **12** (5.7 g, 46%) as a pale yellow oil. The diastereomeric ratio was 89:11 (determined by NMR analysis). ^{2}H NMR of **11** δ 1.01 (D-2_{ax}), 1.46 (D-1), 3.47 (D-7 = CD_2OH). Low signals due to the occurrence of the *cis*-isomer **12** are present in the spectrum (Fig. 1).

4.4.2. Reduction of synthetic (*R*)-(+)-perillaldehyde. The same procedure described above was performed on (*R*)-(+)-perillaldehyde **8** (10 g, 67 mmol) to give a 79:21 mixture of *cis*/*trans*-isomers **12** and **11** (4.4 g, 43%). ^{2}H NMR of **12** δ 1.53 and 1.62 (D-2_{ax} + D-2_{eq}), 1.79 (D-1), 3.60 (D-7 = CD_2OH). Strong signals due to the occurrence of the *trans*-isomer **11** are clearly visible in the spectrum (Fig. 1).

Acknowledgements

The authors would like to thank COFIN-MURST for partial financial support.

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