Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1589–1596

TETRAHEDRON: *ASYMMETRY*

On the baker's yeast mediated transformation of α-bromoenones. Synthesis of (1*S*,2*R*)-2-bromoindan-1-ol and (2*S*,3*S*)-3-bromo-4-phenylbutan-2-ol

Josephina Aleu, Giovanni Fronza, Claudio Fuganti, Valentina Perozzo and Stefano Serra *

Dipartimento di Chimica del Politecnico, Centro CNR per lo Studio delle Sostanze Organiche Naturali, Via Mancinelli 7, I-20131 Milano, Italy

Received 11 March 1998; accepted 26 March 1998

Abstract

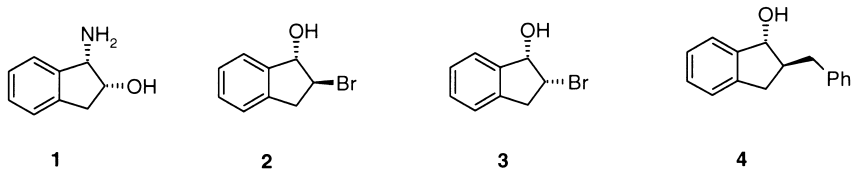
Fermenting baker's yeast converts α-bromo substituted enones **7** and **10** into enantiomerically pure (1*S*,2*R*)-2-bromoindan-1-ol **3** and (2*S*,3*S*)-3-bromo-4-phenylbutan-2-ol **11**, respectively, through the intermediacy of the corresponding saturated ketones. Structurally related **16** provides the (2*R*)-allylic alcohol **17** prevalently.

1. Introduction

The preparation of optically active forms of 1-aminoindan-2-ol has recently received interest mainly because of the utility of the (1*S*,2*R*)-enantiomer **1** (Fig. 1) in the synthesis of the HIV protease inhibitor indinavir.[1] To this end, the methodologies applied include the asymmetric epoxidation of indene followed by ammonia treatment,[2,3] the chemical resolution of the racemic material,[4] and the use of biological methods leading to a variety of enantiomerically pure forms of advanced intermediates.[5–9] These also include the two enantiomeric forms of both diastereoisomers of indene bromohydrin. Accordingly, (1*S*,2*R*)-**3** is accessible by enzymic benzylic hydroxylation of prochiral 2-bromoindane[6] whereas the (1*S*,2*S*)-diastereoisomer **2** can be obtained by kinetic resolution in the enzymic acylation of the racemic modification[9] or by microbial reduction of 2-bromoindan-1-one **5** (Fig. 2) with *Cryptococcus macerans*.[10] The latter method seems of limited preparative significance because of the reported seven days incubation period. The 55% isolated yield suggests, however, at least partial racemization in the culture medium of the enantiomeric form of the ketone not accepted by the reducing enzyme(s).

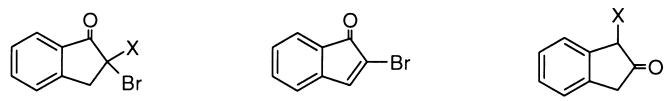
* Corresponding author.

0957-4166/98/$19.00
PII: S0957-4166(98)00128-1



1 2 3 4

Fig. 1.



5 X = H
6 X = Br

7

8 X = Br
9 X = H

Fig. 2.

2. Results and discussion

In light of the known ability of fermenting baker's yeast to reductively transform a variety of cyclic carbonyl compounds into optically active carbinols,[11] we decided to study a baker's yeast mediated approach to optically active indene bromohydrin, using prochiral 2-bromo-2-inden-1-one **7** as a substrate instead of the racemic ketone **5**. The mode of baker's yeast transformation of α,β-unsaturated ketones is not fully predictable.[12] Depending upon the nature of the substituents at relevant positions in the molecule, α-enones provide enantiomerically pure allylic alcohols, saturated ketones, saturated carbinols or mixtures thereof.[13] Accordingly, a set of structurally related products to **7** was submitted to baker's yeast reduction which provided highly functionalized enantiomerically pure products of potential synthetic interest and we outline the results here.

Thus, the unsaturated bromoketone **7** was prepared from 2,2-dibromoindan-1-one **6**[14] upon treatment with triethylamine at room temperature. The product, obtained as an amorphous solid, is rather unstable, but can be kept for weeks when cooled. From the incubation of **7** (3 g) in fermenting baker's yeast (250 g in 1 L tap water) after 24 h, a crystalline bromohydrin was isolated as the only transformation product m.p. 106–109°C (from hexane), $[\alpha]_D^{20}=-59$ (c 4.5, $CHCl_3$) in 75% yields, 99% *ee* by HPLC analysis on Chiracel OD. This material was shown to be (1*S*,2*R*)-**3** by comparison with an authentic sample.[6] The analysis of samples withdrawn from the incubation mixture at different time intervals indicates that **7** is transformed into **3** via the intermediacy of the ketone **5**. The allylic alcohol derived from the reduction of the carbonyl group of **7** was not detected. We were unable to determine the enantiomeric composition of intermediate **5** produced by reduction of **7**, because attempts at separation of the two enantiomeric forms of the bromoketone by HPLC on Chiracel OD failed. Accordingly, the production of (1*S*,2*R*)-**3** might be a consequence of the direct reduction by baker's yeast of enantiomerically pure (2*R*)-**5**, produced in the enzymic double bond saturation, or of the kinetic preference for the (2*R*)-enantiomer of a ketone which rapidly racemizes in the transformation medium.

Indeed, direct incubation of **5** with baker's yeast provided enantiomerically pure **3** in over 85% isolated yield, thus supporting the latter view. In an experiment in which the incubation of **5** was interrupted at ca. 50% conversion, the recovered material, separated from **3** by SiO_2 column chromatography, was shown by ^1H NMR studies in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) to contain ca. 20% excess of a single enantiomer, conceivably corresponding to the (*S*)-material. In ethanolic solution, the latter material showed a negative optical rotation, which, however, decreased on standing. Product **5** is a better substrate for baker's yeast than **7**. It provided enantiomerically pure **3** in 16 h incubation at 6 g/L in the presence of 250 g of baker's yeast.

Thus, in *C. macerans* and baker's yeast, the reduction of 2-bromoindanone occurs with formal hydride delivery onto the *re*-face of the carbonyl group to produce the (1*S*)-configured carbinol, but the preferred absolute configuration of the substrate changes from (*S*) to (*R*), respectively, leading eventually to the enantiomerically pure diastereoisomeric materials **2** and **3**.

The dibromoketone **6** was also submitted to the action of baker's yeast. The substrate was incubated at 1 g/L, due to the low solubility, and provided enantiomerically pure **3** in 30% yield. From the incubation mixture unreacted **6** was also recovered (35%). At present, no indications are available on the mechanism of the formal removal of one bromine atom from the framework of **6** during the yeast treatment. However, it is also worth mentioning the conversion of 1-bromoindan-2-one **8**, treated with baker's yeast (3 g/L), as above, within 4 h into indan-2-one **9** and indan-2-ol, in ca. 4:1 ratio.

Interestingly enough, baker's yeast operates on indan-1-one derivatives structurally related to the above materials in a different way. Thus, 2-benzylideneindan-1-one[3] is rapidly reduced to the saturated ketone. Only at long incubation time is there the formation of minute amounts of a carbinol, m.p. 98–100°C, $[\alpha]_D^{20}$=+12.6 (c 1, $CHCl_3$), enantiomerically pure on the basis of HPLC analysis. The material was assigned the *anti* relative configuration depicted in structural formula **4**, while the absolute configuration remains undefined. The relative stereochemistry of **4** was determined from the comparison of the ^{13}C NMR spectra of the two diastereoisomers obtained by $NaBH_4$ reduction of the 2-benzylideneindan-1-one. On going from the *syn* to the *anti* configuration, the carbons C-1 and C-2 are shifted downfield by 4.6 and 5.4 ppm respectively; similar chemical shift variations were observed between the *syn* and *anti* 2-methyl-1-cyclopentanols, thus allowing by comparison the assignment of the relative configuration of **4**. The saturated ketone isolated from the incubation mixture was devoid of optical activity. Moreover, 3-aryl substituted inden-1-ones are converted by baker's yeast into the corresponding (*S*)-allylic alcohols, as recently reported in the context of a synthetic study of enantiomerically pure antihypertensive therapeutic agents.[15]

The study on the mode of yeast reduction of α-enones was subsequently extended to acyclic **10**.[16] The latter product (Fig. 3) bears, as compound **7**, α-bromo and β-phenyl substituents, but at opposite sites of the double bond, in an acyclic framework. The bromoenone **10** proved to be a good substrate for baker's yeast. It is transformed at 8 g/L in the presence of 400 g of yeast into the saturated carbinol **11**, oil, $[\alpha]_D^{20}$=−13.6 (c 2.2, $CHCl_3$), in 80% isolated yields. The (2*S*,3*S*)-configuration depicted in structural formula **11** and the substantial enantiomeric purity are assigned on the basis of the following evidence. The bromoalcohol **11** was first converted by $LiAlH_4$ treatment in refluxing THF into enantiomerically pure (2*S*)-4-phenylbutan-2-ol **12**, $[\alpha]_D^{20}$=+13.8 (c 3.8, $CHCl_3$), identical with the material obtained from (−)-betuligenol[17,18] by removal of the phenolic hydroxyl group.[19,20] Subsequently, product **11**, upon basic treatment, was converted into an epoxide, $[\alpha]_D^{20}$=−16.7 (c 8.2, $CHCl_3$), which upon $LiAlH_4$ treatment in refluxing THF provides (2*S*)-1-phenylbutan-2-ol **14**, $[\alpha]_D^{20}$=+18.5 (c 5.3, AcOEt) and +22 (c 1.5, Et_2O) (lit.[21] for the (*R*)-enantiomer, −21.7, Et_2O), shown to be enantiomerically pure by HPLC analysis, containing a minute amount of (2*S*)-**12**. With the expectation that epoxide formation took place with inversion of configuration at the carbon atom from which the bromine atom is displaced, the present results support the (2*S*,3*S*)-configuration for **11**, the bromoalcohol, and structure **13** for the epoxide derived from the latter upon basic treatment.

In the yeast reduction of **10**, the only detectable species present in the incubation mixture were the starting material and the saturated carbinol **11**, with no trace of the allylic carbinol. This observation suggests that the rate limiting process is the saturation of the double bond of the α-enone. The saturated ketone, once formed, is rapidly reduced to the bromoalcohol actually isolated. The activating function of the carbonyl group towards the enzymic double bond saturation is further supported by the following experiments. The synthesis of **10** proceeds by sodium acetate induced dehydrobromination of the crude

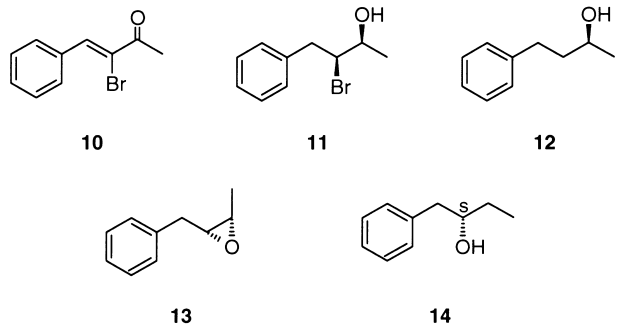


Fig. 3.

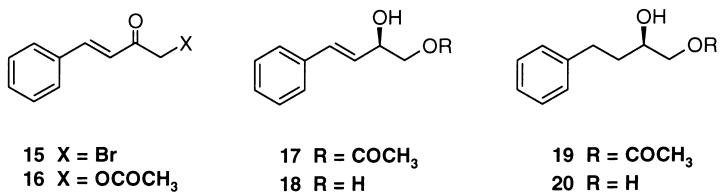


Fig. 4.

dibromoketone obtained by treatment with 1 mol. equiv. of bromine benzalacetone in $CHCl_3$ solution.[16] In our hands, the process provided, as well as **10**, substantial quantities of **16** (Fig. 4), conceivably formed by the action of acetate on **15**, formed by α-bromination of benzalacetone. Baker's yeast incubation of **16** provides a ca. 3:1 mixture of the unsaturated and saturated (2*R*)-carbinols **17** and **19**. The stereochemical assignment was made by converting the mixture, by catalytic hydrogenation followed by basic hydrolysis, into (2*R*)-4-phenylbutan-1,2-diol **20**, identical in every respect, including specific rotation, to the product obtained from commercial (2*R*)-ethyl-2-hydroxy-4-phenylbutyrate[22] by $LiAlH_4$ reduction. The enantiomerically pure allylic (2*R*)-diol **18** can be separated from **20** by fractional crystallization from hexane.

The enone **16** in baker's yeast undergoes carbonyl reduction to provide the allylic alcohol **17** or saturation of the double bond, followed by carbonyl reduction, to yield eventually the saturated alcohol **19**. Once the transformation took place, the ratio **17**/**19** is not altered over time, and, as the incubation proceeds further, the only noticeable operation is the hydrolysis of the acetate ester to provide **18** and **20**, respectively. Moreover, the synthetic carbinol **17**, prepared from **16** by $NaBH_4$ reduction at low temperature and neutral pH in order to avoid acetate hydrolysis, on prolonged yeast incubation undergoes only ester hydrolysis to racemic **18**. Seen together, these results thus show that baker's yeast, although on the chemical scene for many years, still exhibits unpredictable behaviour towards structurally related substrates, as here indicated by the different mode of transformation of **7**, **10** and **16**. However, these processes make available highly functionalized enantiomerically pure products of synthetic potential, such as the bromoalcohol **3**, useful in the synthesis of (1*S*,2*R*)-1-aminoindan-2-ol, **11**, **13** and the allylic α-acetoxy carbinol **17**.

3. Experimental

3.1. General procedure for the baker's yeast transformation

In a 2 L three-necked round-bottomed flask, a mixture is made up composed of 250 g baker's yeast, 100 g of D-glucose and 1 L of tap water at 38–40°C. After 10 min stirring, the substrate dissolved in the minimum amount of ethanol is added dropwise. The stirring is continued at the above temperature and at the end of the process the mixture is poured into 2 L of acetone:ethyl acetate (1:1). After stirring for 2 h, the mixture is filtered through a large Buchner funnel on a Celite pad, which is later washed with the same solvent. The aqueous phase is extracted twice with 0.5 L of ethyl acetate. The residue obtained upon evaporation of the dried combined organic extracts is purified by column chromatography.

HPLC analyses were performed on a chiral column (Chiracel OD, Daicel, Japan): 254 nm, 0.6 mL/min, hexane:isopropanol (9:1), (1*S*,2*R*)-**3** R_t=13.96 min; (1*R*,2*S*)-**3** R_t=14.56 min; (+)-**4** R_t=12 min, (−)-**4** R_t=26 min; (2*S*,3*S*)-**11** R_t=10.78 min; (*R*)-**12** R_t=11.00 min; (*S*)-**12** R_t=15.44 min; (2*S*)-**17** R_t=10.65; (2*R*)-**17** R_t=11.4 min (flux: 1 mL/min); (2*S*)-**19** R_t=14.32 min; (2*R*)-**19** R_t=15.7 min (flux: 1 mL/min); (2*S*)-**18** R_t=12.8; (2*R*)-**18** R_t=17.45 min (flux: 1 mL/min); (2*S*)-**20** R_t=14.62 min; (2*R*)-**20** R_t=19.57 min (flux: 1 mL/min).

3.2. 2-Bromoinden-1-one *7*

2,2-Dibromoindan-1-one **6**[14] (15 g, 52 mmol) in THF (100 mL) was treated with triethylamine (40 mL) at room temperature for 24 h. The mixture was diluted with ethyl acetate (150 mL) and washed with cold water, 5% HCl and 1% $NaHCO_3$. The dried organic phase was concentrated under reduced pressure and the residue purified by SiO_2 column chromatography with increasing amounts of ethyl acetate in hexane to give **7**, an amorphous solid, in 63% yield (7 g, 33 mmol). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.01 (1H, d, J=7.5 Hz), 7.15–7.25 (1H, m), 7.30–7.38 (1H, m), 7.45 (1H, d, J=7.5 Hz), 7.61 (1H, s); *m/z* (EI): 210 (M^++2, 27), 208 (M^+, 30), 182 (M^++2−CO, 32), 180 (M^+−CO, 35), 129 (M^+−Br, 78), 101 (100), 98 (36), 74 (48).

3.3. (1S,2R)-2-Bromoindan-1-ol *3* from *5* and *7*

Baker's yeast reduction of **7** (3 g/L) and **5** (6 g/L) provided **3**, m.p. 107–109°C and 108°C, respectively (from hexane), $[\alpha]_D^{20}$=−59 (c 4.5, $CHCl_3$) and −60, respectively (lit[6] $[\alpha]_D^{20}$=−61). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.41 (2H, m), 4.95 (2H, m), 7.20–7.35 (4H, m); *m/z* (EI): 214 (M^++2, 10), 212 (M^+, 15), 197 (M^++2−OH, 12), 195 (M^+−OH, 10), 133 (M^+−Br, 100), 116 (22), 103 (7), 77 (10). The two materials were shown by the above HPLC analysis to possess 0.99 *ee*.

3.4. (2S)-2-Bromoindan-1-one *5* from baker's yeast reduction of rac-*5*

Baker's yeast reduction of **5** (6 g/L) was interrupted at ca. 50% conversion. The unchanged product was separated from carbinol **3** by column chromatography (10% AcOEt in hexane) and submitted to ^{1}H NMR studies in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)camphorato]europium (III): ^{1}H NMR of remaining **5** ($CDCl_3$): δ 3.43 (1H, dd, J=3.0 and 17.9 Hz), 3.85 (1H, dd, J=7.4 and 17.9 Hz), 4.68 (1H, d, J=3.0 and 7.4 Hz), 7.46 (2H, m), 7.67 (1H, m), 7.85 (1H, d, J=7.7 Hz). Upon addition of the Eu(III) complex to the solution, many signals are doubled, the best separation occurring for the aromatic hydrogen *peri* to the carbonyl group (originally at 7.85 ppm) which gives rise to two signals at 8.29 (minor enantiomer) and 8.19 (major enantiomer) ppm. The two signals were integrated giving ca. 20% excess of a single enantiomer.

3.5. anti-*2-Benzylindan-1-ol* ***4*** *from benzylideneindan-1-one*

2-Benzylideneindan-1-one[3] was submitted (1 g/L) to the action of fermenting baker's yeast. The usual work-up, after 62 h incubation, provided, after separation on a SiO_2 column with hexane:AcOEt (9:1), 2-benzylindan-1-one, devoid of optical activity in chloroform solution, and the crystalline carbinol **4**, m.p. 98–100°C (from hexane), $[\alpha]_D^{20}$=+12.6 (c 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.43–2.62 (2H, m), 2.70–2.85 (1H, m), 2.90–3.14 (2H, m), 4.94 (1H, d, J=5.6 Hz), 7.10–7.40 (9H, m); ^{13}C NMR ($CDCl_3$): δ 35.80 (CH_2), 39.31 (CH_2), 52.21 (CH), 80.84 (CHOH), 123.97 (1C), 124.78 (1C), 126.17 (1C), 126.78 (1C), 128.16 (1C), 128.55 (2C), 128.92 (2C), 140.64 (1C), 141.55 (1C), 144.56 (1C); *m/z* (EI): 224 (M^+, 20), 206 (M^+-H_20, 40), 132 (41), 115 (31), 91 (100), 77 (30). Found: C, 85.79; H, 7.13; $C_{16}H_{16}O$ requires C, 85.68; H, 7.19. *syn*-2-Benzylindan-1-ol (obtained by $NaBH_4$ reduction of benzylideneindan-1-one followed by separation of the two diastereoisomers), ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80 (1H, s br), 2.51–2.79 (4H, m), 3.02 (1H, dd, J=5.5 and 13.2 Hz), 4.88 (1H, d, J=5.3 Hz), 7.10–7.30 (9H, m); ^{13}C NMR ($CDCl_3$): δ 34.92 (CH_2), 35.84 (CH_2), 46.84 (CH), 76.23 (CHOH), 124.75 (1C), 124.92 (1C), 125.84 (1C), 126.66 (1C),128.35 (2C), 128.43 (1C), 128.87 (2C), 141.30 (1C), 143.38 (1C) 144.75 (1C).

3.6. *Baker's yeast incubation of 2,2-dibromoindan-1-one* ***6***

Product **6**[14] (1 g/L) on yeast treatment provides, after usual work-up and chromatographic separation of the crude extract, unreacted material (35%) and product **3** (30%), $[\alpha]_D^{20}$=−60 (c 1, $CHCl_3$). The material was shown by HPLC analysis to possess 99% *ee*.

3.7. *(2S,3S)-3-Bromo-4-phenylbutan-2-ol* ***11***

Baker's yeast reduction of **10**[16] (8 g/1 L, 0.4 kg baker's yeast) provided **11** (6.5 g, 80%) as a colourless oil, $[\alpha]_D^{20}$=−13.6 (c 2.2, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.30 (3H, d, J=6.5 Hz), 3.10–3.45 (2H, m), 3.70 (1H, m), 4.12–4.25 (1H, m), 7.15–7.45 (5H, m); *m/z* (EI): 230 (M^++2, 1), 228 (M^+, 1), 148 (M^+-Br, 25), 131 (77), 105 (58), 91 (100), 78 (38); IR (cm^{-1}) 3422, 2976, 1496, 1455, 1376, 751, 700. Found: C, 52.29; H, 5.80; Br, 34.99; $C_{10}H_{13}BrO$ requires C, 52.42; H, 5.72; Br, 34.87.

3.8. *Conversion of (2S,3S)-****11*** *into (2S)-****12***

Compound **11** (1 g, 4.4 mmol) in diethyl ether (10 mL) was added to $LiAlH_4$ (0.2 g, 5.3 mmol) in refluxing diethyl ether (60 mL). After 2 h, ethyl acetate was added to the cooled reaction mixture, followed by cold 5% HCl. The dried organic phase was evaporated and the residue was purified by column chromatography to give carbinol **12** (0.6 g, 4.0 mmol) in 90% yield, purified by bulb-to-bulb vacuum distillation at the water pump (oven temp.: 140°C), 0.98 *ee* by HPLC, $[\alpha]_D^{20}$=+13.8 (c 3.8, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.21 (3H, d, J=6.5 Hz), 1.70–1.83 (2H, m), 2.57–2.88 (2H, m), 3.82 (1H, m), 4.83 (1H, s, OH), 7.15–7.33 (5H, m); *m/z* (EI): 150 (M^+, 32), 132 (M^+-OH, 64), 117 (100), 92 (39), 91 (65), 78 (15); IR (cm^{-1}): 3357, 2928, 1497, 1454, 1375, 746.

3.9. *Conversion of* ***11*** *into the epoxide* ***13***

Product **11** (2 g, 8.8 mmol) in methanol (60 mL) was treated with Na_2CO_3 (5 g, 47 mmol) at room temperature for 30 min. Water was then added and the mixture was extracted with diethyl ether (3×100 mL). The dried organic phase was evaporated under reduced pressure and the residue purified by column chromatography to give the epoxide **13** (1.1 g, 7.4 mmol) in 84% yield, purified by bulb-to-bulb vacuum

distillation at 1 mmHg (oven temperature: 90°C), $[\alpha]_D^{20}=-16.7$ (c 8.2, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 1.04 (3H, d, J=6 Hz), 2.47 (1H, dd, J=14 Hz, J=6 Hz), 2.74 (1H, dd, J=14 Hz, J=6 Hz), 2.77 (1H, m), 2.99 (1H, m), 7.05–7.21 (5H, m); *m/z* (EI): 148 (M^+, 100), 132 (M^+-O, 24), 119 (92), 104 (42), 91 (14), 78 (20); IR (cm^{-1}): 2997, 1497, 1455, 1389, 784. Found: C, 81.21; H, 8.12; $C_{10}H_{12}O$ requires C, 81.04; H, 8.16.

3.10. Conversion of the epoxide **13** into carbinols **14** and **12**

Compound **13** (0.5 g, 3.4 mmol) in diethyl ether (30 mL) was treated with $LiAlH_4$ (0.2 g, 5.3 mmol) at reflux for 4 h to give, after the usual work-up, a mixture of carbinols **14** and **12** in ca. 8:1 ratio (by GLC). Accurate column chromatography allows the separation of alcohol **14** (0.3 g, 2.0 mmol) in pure form, in 58% yield, $[\alpha]_D^{20}=+18.5$ (c 5.3, AcOEt), +22 (c 1.5, Et_2O) (lit.[21] for the (*R*)-enantiomer, −21.7, Et_2O). ^1H NMR (250 MHz, $CDCl_3$): δ 1.00 (3H, t, J=7.5 Hz), 1.49–1.66 (2H, m), 2.64 (1H, dd, J=9, 14.5 Hz), 2.82 (1H, dd, J=5, 14.5 Hz), 3.73 (1H, m), 7.17–7.39 (5H, m); *m/z* (EI): 150 (M^+, 72), 133 (M^+-OH, 18), 92 (100); IR (cm^{-1}) 3370, 2933, 1455, 742, 700.

3.11. Acetoxy ketone **16**

Column chromatography of the crude reaction mixture containing **10**,[16] produced by the action of ethanolic sodium acetate from the crude mixture obtained treating benzalacetone with 1 mol. equiv. of bromine in $CHCl_3$, provides, with increasing amounts of ethyl acetate in hexane, in ca. 4:1 ratio, product **10** and the acetoxy derivative **16**, oil. ^1H NMR (250 MHz, $CDCl_3$): δ 2.21 (3H, s), 4.96 (2H, s), 6.79 (1H, d, J=15 Hz), 7.41 (3H, m), 7.56 (2H, m), 7.68 (1H, d, J=15 Hz). Found: C, 70.71; H, 6.01; $C_{12}H_{12}O_3$ requires C, 70.58; H, 5.92.

3.12. 1-Acetoxycarbinols **17** and **19** and 1,2-diols **18** and **20**

Baker's yeast reduction of **16** (6 g/L) provided after 3 h incubation **17** and **19** in ca. 3:1 ratio, in 80% yield. Continuing the incubation, the ratio of unsaturated to saturated materials was not altered, but there was hydrolysis of the acetate ester to give **18** and **20**. ^1H NMR of **17** in the mixture (250 MHz, $CDCl_3$): δ 2.10 (3H, s), 4.10–4.30 (2H, m), 4.56 (1H, m), 6.18 (1H, dd, J=7, 16 Hz), 6.70 (1H, d, J=16 Hz), 7.15–7.45 (5H, m); of **19** (250 MHz, $CDCl_3$): δ 1.71–1.89 (2H, m), 2.09 (3H, s), 2.57–2.90 (2H, m), 3.54–3.92 (2H, m), 7.10–7.31 (5H, m). The crude incubation mixture, containing **17**–**20**, 5 g, in 30 ml MeOH was treated overnight at room temperature with 0.2 g of sodium methoxide. After that time, the hydrolysis of the acetate group was complete (TLC: hexane:AcOEt=1:1). The reaction mixture was concentrated under vacuum and diluted with water. Two extractions with AcOEt provided an oil, from which diol **18** (50%) separated from hexane, m.p. 134°C, $[\alpha]_D^{20}=-78$ (c 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 1.60–2.05 (2H, m), 4,43 (1H, m), 6.20 (1H, dd, J=5.5, 16.5 Hz), 6.69 (1H, d, J=16.5 Hz), 7.18–7.46 (5H, m). Found: C, 73.29; H, 7.31; $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.37. The material was shown to possess 0.98 *ee* by HPLC analysis and comparison with the racemic material produced from **16** by $NaBH_4$ reduction, followed by ester hydrolysis under basic conditions. Compounds **17**, **18** and **19** have been also characterized by GC–MS: *m/z* (EI) (**17**): 146 (M^+-CH_3COOH, 50), 133 (M^+-CH_2OAc, 100), 115 (47), 105 (24), 91 (20); *m/z* (EI) (**18**): 149 (M^+-OAc, 10), 130 (40), 117 (20), 104 (30), 91 (100); *m/z* (EI) (**19**): 164 (M^+, 6), 146 (M^+-H_2O, 5), 133 (100), 115 (58), 103 (21), 91 (23).

3.13. (2R)-4-Phenylbutan-1,2-diol **20**

The mixture of the compounds **18** and **20** from baker's yeast incubation (0.3 g) in AcOEt (50 mL) was hydrogenated at normal pressure in the presence of 10% Pd/C (0.1 g) to give **20**, colourless oil, $[\alpha]_D^{20}=-13.2$ (c 4.5, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.55–1.90 (2H, m), 2.60–2.90 (2H, m), 3.40–3.55 (2H, m), 3.56–3.75 (1H, m), 7.10–7.35 (5H, m); *m/z* (EI): 166 (M^+, 2), 148 (M^+-H_2O, 23), 130 (8), 117 (30), 104 (10), 91 (100); IR (cm^{-1}): 3358, 2931, 1497, 1455, 1389, 700. Found: C, 72.35; H, 8.45; $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49. 0.99 *ee* by HPLC analysis. This material was identical in every respect to the product obtained when (2*R*)-ethyl-2-hydroxy-4-phenylbutyrate (Fluka) was reduced with $LiAlH_4$ in refluxing THF, followed by the usual work-up.

Acknowledgements

The financial support of Progetto Finalizzato CNR Biotecnologie is acknowledged.

References

1. Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, O. M.; Roth, E.; Sardana, V. V.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotlib, L.; Holloway, M. K.; Lin, J.; Chen, I.-W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. *Proc. Natl Acad. Sci., USA* **1994**, *91*, 4096.
2. Senanayake, C. H.; DiMichele, L. M.; Liu, J.; Fredenburgh, L. E.; Ryan, K. M.; Roberts, F. E.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett*. **1995**, *36*, 6811, and references therein.
3. Levin, N.; Graham, B. E.; Kolloff, H. G. *J. Am. Chem. Soc*. **1944**, *66*, 380.
4. Lehr, P.; Billich, A.; Brigitte, C.; Ettmayer, P.; Scholz, D.; Rosenwirth, B.; Gstach, H. *J. Med. Chem.* **1996**, *39*, 2060 and references therein.
5. Didier, E.; Loubinoux, B.; Ramos Tombo, G. M.; Rihs, G. *Tetrahedron* **1991**, *47*, 4941.
6. Boyd, D. R.; Sharma, N. D.; Bowers, N.; Goodrich, P. A.; Groocock, M. R.; Blacker, A. J.; Clarke, D. A.; Howard, T.; Dalton, H. *Tetrahedron: Asymmetry* **1996**, *7*, 59.
7. Mitrochkine, A.; Eydoux, F.; Martres, M.; Gil, G.; Heumann, A.; Reglier, M. *Tetrahedron: Asymmetry* **1995**, *6*, 59.
8. Ghosh, A. K.; Kincaid, J. F.; Haske, M. G. *Synthesis* **1997**, 541.
9. Igarashi, Y.; Otsutomo, S.; Harada, M.; Nakano, S.; Watanabe, S. *Synthesis* **1997**, 549.
10. Imuta, M.; Ziffer, H. *J. Org. Chem*. **1978**, *43*, 4540.
11. Servi, S. *Synthesis* **1990**, 1.
12. Fogliato, G.; Fronza, G.; Fuganti, C.; Lanati, S.; Rallo, R.; Rigoni, R.; Servi, S. *Tetrahedron* **1995**, *51*, 10231. Fronza, G.; Fuganti, C.; Grasselli, P.; Lanati, S.; Rallo, R.; Tchilibon, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2927.
13. Fuganti, C.; Grasselli, P.; Mendozza, M.; Servi, S.; Zucchi, G. *Tetrahedron* **1997**, *53*, 2617.
14. House, H. O.; McDaniel W. C. *J. Org. Chem*. **1977**, *42*, 2155.
15. Clark, W.; Lantos, I.; Maloney, A. P. *Biotrans '97*, La Grande Motte, France, Sept. 22–26, 1997, pp. 1–34.
16. Cromwell, N. H. *J. Am. Chem. Soc.* **1940**, *62*, 3470.
17. Parmar, V. S.; Vardhan, A.; Taneja, P.; Sinha, R.; Patnaik, G. K.; Tripathi, S. C.; Boll. P. M.; Larsen, S. *J. Chem. Soc., Perkin Trans 1* **1991**, 2687.
18. Fuganti, C.; Mendozza, M.; Joulain, D.; Minut, J.; Pedrocchi-Fantoni, G.; Piergiann, V.; Servi, S.; Zucchi, G. *J. Agric. Food Chem.* **1996**, *45*, 3616.
19. Musliner, W. J.; Gates Jr., J. W. *Org. Synth*. **1971**, *51*, 82; John Wiley & Sons, Ed. Benson, R. E.
20. The details of this conversion will be published separately.
21. Levene, L. A.; Walti, A. *J. Biol. Chem*. **1931**, *94*, 367.
22. Urbach, H.; Henning, R. *Tetrahedron Lett*. **1984**, *25*, 1143.