On the Mode of Bakers' Yeast Transformation of 3-Chloropropiophenone and Related Ketones. Synthesis of (2*S*)-[2-^{2}H]Propiophenone, (*R*)-Fluoxetine, and (*R*)- and (*S*)-Fenfluramine

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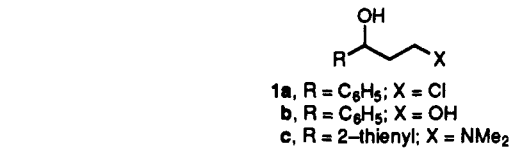
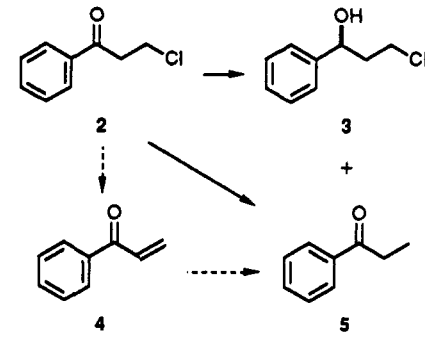
Yeast treatment of 3-chloropropiophenone (**2**) affords the expected (1*S*)-3-chloro-1-phenylpropan-1-ol (**3**) as well as ca. 30% of propiophenone (**5**). The conversion of **2** into **5** is accompanied by formal elimination of hydrochloric acid, followed by yeast saturation of the double bond of the intermediate phenyl vinyl ketone (**4**). Monodeuteriopropiophenone formed via yeast treatment from α,α-dideuterio-3-chloropropiophenone (**8**) was shown to possess the 2*S* configuration **10** by conversion into [2-^{2}H]-(1*R*,2*S*)-1-phenylpropan-1-ol (**13**), whose stereochemistry was assigned by comparison of its NMR properties with those of the [2-^{2}H]-(1*S*,2*S*) diastereoisomer **19** synthesized from yeast-generated (1*R*,2*S*)-1-phenylpropane-1,2-diol (**15**). Whereas product **3** is converted into (*R*)-fluoxetine (**31**), 2*S* alcohol **24**, obtained in the yeast reduction of the ketone **22** is transformed into (*R*)-fenfluramine (**29**) and into its enantiomer (**26**).

The synthesis of the enantiomeric forms of 3-substituted 1-arylpropan-1-ol **1** has recently received attention in connection with the preparation of optically active forms of the serotonine-uptake inhibitors fluoxetine,[1-3] tomoxetine,[1,2] nisoxetine,[1] and LY248686.[4] Whereas **1b** was obtained from cinnamyl alcohol through enantioselective epoxidation,[2] followed by regiospecific hydride ring opening, **1a** and **1c** have been prepared from the corresponding ketones by hydride reduction using boron reagents[1,3] or chirally modified lithium aluminum hydride.[4] In light of the well-documented capacity of bakers' yeast to reduce monsymmetrically substituted ketones to the corresponding carbinols[5] of high enantiomeric purity, we applied the preparation of chiral **1a** to the yeast reduction of 3-chloropropiophenone (**2**). In this paper we report on a study of the mode of yeast reduction of 3-chloropropiophenone (**2**) and of related products and of the stereochemistry of the conversion of **2** into propiophenone (**5**), which takes place along with the formation of 3-chloro-1-phenylpropan-1-ol. Although previous experiments[6] on the mode of reduction of 1-phenyl-1,3-butanedione with bakers' yeast indicated that the prevalent transformation product was (*S*)-3-hydroxy-1-phenyl-1-butanone, thus suggesting the low aptitude of this microbial system to reduce the carbonyl group adjacent to the aromatic ring of 3-substituted aryl ketones, we observed, under our experimental conditions, a rather rapid consumption of 3-chloropropiophenone (**2**) on yeast treatment. However, analytical studies indicated that the disappearance of the ketone **2** corresponded to the formation of two products, in ca. a 2:1 ratio. The most abundant material was enantiomerically pure (1*S*)-3-chloro-1-phenylpropan-1-ol (**3**), characterized on the basis of optical measurements and comparison with an authentic sample, whereas the second product was propiophenone (**5**). In light of the latter result, we carried out blank experiments, keeping 3-chloropropiophenone (**2**) in acidic medium (pH 5–5.5, the pH of the fermenting yeast) at ca. 30 °C for 16–24 h, but the product was recovered unaltered quantitatively. We thus expected that the formation of propiophenone (**5**) from 3-chloropropiophenone (**2**) in bakers' yeast might be the consequence of an (acid-catalyzed chemical or enzymic) elimination of hydrochloric acid to form as an intermediate phenyl vinyl ketone (**4**), followed by (enzymic) saturation of the carbonyl-activated double bond of the latter (Scheme I). In order to verify this hypothesis, we performed experiments with 2-dideuterated 3-chloropropiophenone (**8**) to determinate the fate of the labels in the products present in the reaction mixture and the stereochemistry of the surviving deuterium atom in biogenerated propiophenone (**5**). To this end, [2-^{2}H$_2$]-3-

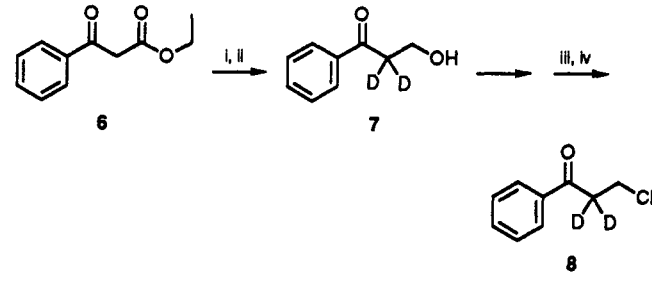


1a, R = C_6H_5; X = Cl
b, R = C_6H_5; X = OH
c, R = 2-thienyl; X = NMe_2

Scheme I



Scheme II[a]



[a] (i) $D_2O/Et_3N/THF$; (ii) $LiAlH_4$; (iii) Ph_3P/CCl_4; (iv) MnO_2.

(1) Srebnik, M.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1988**, *53*, 2916.
(2) Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 4081.
(3) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207.
(4) Deeter, J. K.; Frazier, J.; Staten, G.; Staszak, M.; Weigel, L. *Tetrahedron Lett.* **1990**, *31*, 7101.
(5) Servi, S. *Synthesis* **1990**, 1.
(6) Chenevert, R.; Thiboutot, S. *Can. J. Chem.* **1986**, *64*, 1599. Fauve, A.; Veschambre, H. *J. Org. Chem.* **1988**, *53*, 5215.

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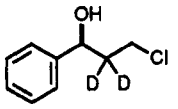
chloropropiophenone (8) was prepared from ethyl benzoylacetate (6) (Scheme II). Base-catalyzed hydrogen exchange, using deuterated water in tetrahydrofuran and triethylamine, gave rise to a material shown by NMR studies to contain ca. 80% dideuterated species. This material, on $LiAlH_4$ reduction, afforded in moderate yield the dideuterated 1,3-diol 7, converted into desired 8, containing 75–80% dideuterated species, by sequential treatment with 1 molar equiv of triphenylphosphine in carbon tetrachloride and activated manganese dioxide. Yeast incubation of 8 and extraction of the reaction mixture when some 8 was still present afforded 8, retaining at position 2 all the deuterium originally present, dideuterated 7, and monodeuterated propiophenone (0.75 *d* at position 2). This material was assigned the stereochemistry depicted in structural formula 10 on the basis of the following experiments.



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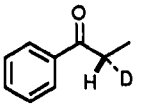

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Firstly, we attempted to determine the chirality of the biogenerated monodeuteriopropiophenone from the examination of the NMR spectra taken in the presence of a chiral shift reagent. In fact, the two methylene protons of propiophenone (5) are internally enantiotopic and the addition of a chiral shift reagent should induce in principle some chemical shift difference between them.[7] However, this experiment, employing tris[(3-heptafluoropropyl)-hydroxymethylene-*d*-camphorato]europium(III), was unsuccessful. Nevertheless, the two hydrogen atoms of the prochiral center at C-2 of 1-phenylpropan-1-ol and of its acetyl derivative resonate at different chemical shifts, thus allowing a discrimination between the *pro-R* and *pro-S* methylene protons. We cannot assign the two protons on the basis of the vicinal coupling coupling constants $J(1,2)$ and $J(1,2')$, since they range from 6 to 7 Hz, indicating that the molecule does not have a single conformational preference.

We thus decided to determinate the stereochemistry of the deuterium retained in position 2 of propiophenone (10) biogenerated in bakers' yeast from dideuterio-3-chloropropiophenone (8) (a) by converting the ketone 10 into chiral forms of [2-^{2}H]-1-phenylpropan-1-ol and (b) determining the diastereoisomeric composition through comparison with authentic samples of known stereochemistry. The first goal was easily achieved (Scheme III) by sodium borohydride redn. of 10 to 11, converted, in turn, into the acetyl derivative with acetic anhydride and pyridine. The later material was selectively hydrolyzed[8] to the 1*R* carbinol 13, using lipase from *Pseudomonas fluorescens* at pH 7. Carbinol 13 was shown by GLC analysis on a chiral column[9] to be enantiomerically pure, whereas the acetyl derivative 12 indicated lower optical purity. At this point [2-^{2}H]-(1*R*)-1-phenylpropan-1-ol (13) was chemically acetylated and submitted to deuterium NMR analysis. The acetyl derivative was preferred over the alcohol for this analysis, since it exhibits a more marked chemical shift difference. The biogenerated material contained, as illustrated in Figure 1, over 90–95% of a single diastereoisomer, thus supporting a stereospecific hydrogen addition in the saturation of α-deuterio phenyl vinyl ketone, invoked as an intermediate in the conversion of 8 into 10. The assignment of the absolute stereochemistry of the deuterium atom remaining at position 2 of 10 requires, as indicated above, the availability of 1-phenylpropan-1-ol samples monodeuterated in position 2 of unambiguously defined diastereoisomeric composition. This goal was achieved with the use of bakers' yeast in the key step. Indeed, starting material in the synthesis of the required reference product was the 1*R*,2*S* diol 15,[10] ac-

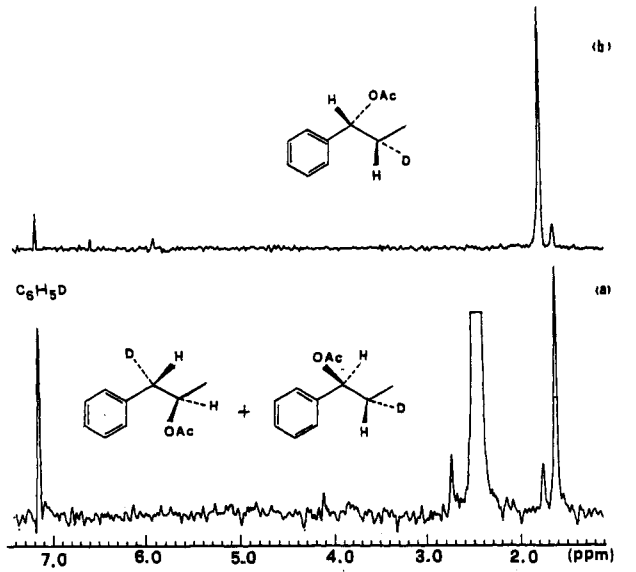
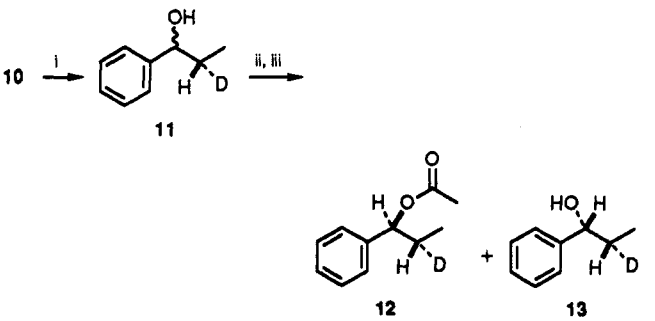


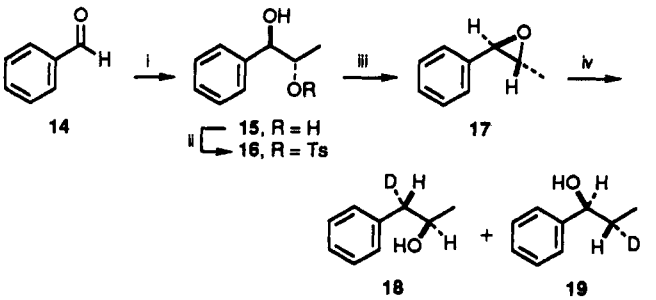
Figure 1. Deuterium NMR spectrum in C_6D_6 of (a) 9:1 mixture of acetyl derivatives of [1-$^2H_1$]-1-phenylpropan-2-ol and [2-$^2H_1$]-1-phenylpropan-1-ol, from the deuteride reduction of the epoxide 17, and (b) acetyl derivative of [2-$^2H_1$]-1-phenylpropan-1-ol, from propiophenone 10.

Scheme III[a]



[a] (i) $NaBH_4$/MeOH; (ii) Ac_2O/pyridine; (iii) lipase SAM-2, pH 7.

Scheme IV[a]



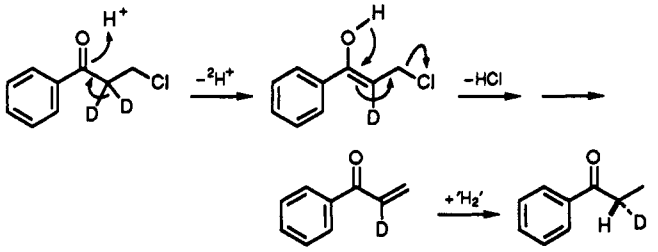
[a] (i) Bakers' yeast/D-glucose; (ii) TsCl/pyridine; (iii) MeONa/MeOH; (iv) $LiAlD_4$.

(7) Frazer, R. R.; Petit, M. A.; Miskow, M. *J. Am. Chem. Soc.* 1972, *94*, 3253.

(8) Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* 1988, 598.

(9) Megadex I, fused silica capillary column coated with permethylated β-cyclodextrine, Mega srl, Legnano, Italy.

Scheme V

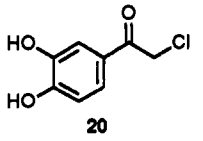


cessible from benzaldehyde (**14**) in bakers' yeast actively fermenting on D-glucose in a well-studied[11] two-step enzymic sequence, involving decarboxylative incorporation of pyruvate to give (1*R*)-1-phenyl-1-hydroxypropan-2-one, followed by stereospecific reduction to the anti diol actually isolated (Scheme IV). The material, separated from the accompanying benzyl alcohol by chromatography, was shown to be diastereoisomerically pure by GLC analysis of its isopropylidene derivative, whereas the substantial enantiomeric purity was further confirmed through the GLC analyses of the derived products **18** and **19** indicated below. Thus, the diol **15**, on treatment with 1 molar equiv of 4-toluenesulfonyl chloride in dichloromethane, in the presence of an excess of pyridine, afforded the 2-tosylate **16**, soon converted, on basic treatment, into the 1*R*,2*R* epoxide **17**.[10b] Ring opening of **17**, using lithium aluminum deuteride, afforded a 9:1 mixture of (2*R*)-**18** and (1*S*)-**19**, shown by GLC analysis on a chiral column and by comparison with authentic samples to possess ca. 0.92 ee. The inseparable mixture was chemically converted into the acetyl derivatives and the deuterium NMR spectrum reported in Figure 1 was obtained. The two peaks at 2.48 and 2.75 ppm, in the ratio of 9.5 to 0.5, respectively, belong to the acetylated [1-^{2}H]-1-phenylpropan-2-ol, while the signals at 1.77 and 1.62 ppm, in the ratio of 1 to 9, respectively, belong to the acetylated [2-^{2}H]-1-phenylpropan-1-ol.

Comparison of the signals of the acetyl derivatives of the [2-^{2}H]-1-phenylpropan-1-ol obtained in the present and in the above-mentioned experiments indicates that the two materials are diastereoisomeric. Since in (1*S*)-**19** the deuterium atom arises at position 2 through two inversions of configuration (tosylate elimination and deuteride ring opening) from (1*R*,2*S*)-**15**, it follows that it holds the 2*S* absolute configuration. Therefore, the deuterium atom present at position 2 of the 1*R* alcohol **13** holds the 2*S* stereochemistry, since the acetyl derivatives of the enantiomeric 2-deuterated 1-phenylpropan-1-ols **13** and **19** appear as diastereoisomers in the NMR studies (Figure 1). Thus, the biogenerated monodeuteriopropiophenone possess the structure depicted in **10**. Seen together, the isotopic studies indicate that in bakers' yeast **2** is converted into **5** by (acid-catalyzed) elimination of hydrochloric acid, followed by enzyme-assisted hydrogen addition onto the double bond of the intermediate phenyl vinyl ketone (**4**), holding the hydrogen added at position 2 in the *pro-R* configuration (Scheme V).

Comparison of the mode of saturation of the carbonyl-activated double bond of phenyl vinyl ketone (**4**) with that of the similar process occuring when cinnamaldehyde is transformed into 3-phenylpropanol[12] in bakers' yeast indicates identity of stereochemistry, as far as the hydrogen addition to the α position is concerned.

The synthetic potential of bakers' yeast in the preparation of chiral carbinols is illustrated by the following results. Whereas 2-chloro-3',4'-dihydroxyacetophenone (**20**), recently reduced to the corresponding *R* carbinol key



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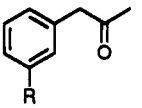
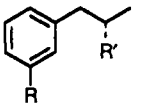
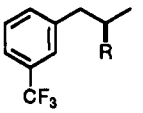


21, R = H
22, R = CF_3

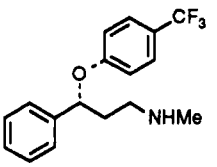
intermediate in the preparation of (*R*)-isopropterenol by means of the borane–(*R*)-oxazaborolidine catalytic[13] system, was not reduced by bakers' yeast, perhaps also because of the very low solubility, the ketones **21** and **22**, in which the carbonyl group is shifted one carbon away from the aromatic ring with respect to propiophenone (**5**) are readily reduced to the 2*S* carbinols **23** and **24**. Absolute





23, R = H; R' = OH
24, R = CF_3; R' = OH
25, R = CF_3; R' = OTS
26, R = CF_3; R' = $NHCH_2CH_3$

27, R = N_3
28, R = NH_2
29, R = $NHCH_2CH_3$
30, R = OH



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configuration and optical purity of yeast-produced **23** are based on GLC analyses[9] and comparison with an authentic sample.[8] Under similar analytical conditions, racemic **24** was not separated on the same chiral capillary column. However, NMR studies on the esters of **24** and of the racemic material with (+)-2-methoxy-2-(trifluoromethyl)phenylacetic acid [(+)-MTPA][14] indicated the optical purity of the former. This was assigned the *S* absolute configuration indicated in **24** because it was converted through the tosylate **25** and azide displacement into **27**, giving, in turn, on $LiAlH_4$ reduction to **28** and final reductive ethylation (*R*)-fenfluramine (**29**).[15] Its enantiomeric purity was confirmed through GLC analysis of the amide with *N*-(trifluoroacetyl)-L-proline and comparison with an authentic sample. The *S* enantiomeric form of this anorectic drug of practical use, particularly difficult to obtain by classical optical resolution, becomes accessible from **24** only via the tosylate **25**, which, on benzoate displacement and hydrolysis, gave rise to **30**. The latter yields, as indicated above, the desired product **26**, in ca. 45% overall yield from the yeast-generated alcohol **24**. The ee value was found to be 0.90 by the above GLC analysis. Finally, (1*S*)-3-chloro-1-phenylpropanol (**2**), obtained in yeast reduction of 3-chloropropiophenone (**2**), was converted into (*R*)-fluoxetine (**31**), following Brown's synthetic pathway,[1] which proceeds under Mitsunobu conditions with inversion of the chiral center present in **2**. The optical purity of **31** confirms the significance of

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(14) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(15) Coquerel, G.; Bonaziz, R.; Brienne, M. J. *Chem. Lett.* **1988**, 1081.

yeast-generated relatively small chiral molecules as starting materials for the synthesis of optically active drugs belonging to quite different structural classes. The relatively simple experimental conditions required for the yeast transformations, the use of tap water and room temperature, the elevated optical yields sometime observed, and the wide substrate tolerance render this methodology a useful complement to the various approaches of asymmetric synthesis based on nonbiological procedures for the obtainment of chiral synthetic intermediates. The unexpected production of propiophenone (5) from 2 and its final obtainment in a chirally deuterated form is further widening the significance of the use of bakers' yeast, extending the application also to the synthesis of molecules that are chiral due to isotopic substitution.

Experimental Section

^2H NMR spectra were obtained with the broadband gated decoupling of the proton nuclei. GC analyses were performed on a chiral column 30 m × 0.25 i.d. Analysis conditions: 75 °C, 1 min; 10 °C/min to 85 °C, then 1 °C/min to 120 °C. Carrier gas: hydrogen. Optical rotations were measured at 23 °C.

Yeast Transformation of 3-Chloropropiophenone (2). In a 20-L glass jar a mixture was made up composed of 2.5 kg of commercial bakers' yeast and 2 kg of D-glucose in 10 L of tap water at 32 °C. As the fermentation started, 50 g of 3-chloropropiophenone (2) (Fluka) in 50 mL of ethanol was added under stirring. After 16 h at 20 °C, 1 kg of Celite was added, the reaction mixture was filtered on a large Buchner funnel, the solid pad was washed with 2 L of ethyl acetate, and the filtrate was extracted twice with 2-L portions of ethyl acetate. The dried organic phase was evaporated, leaving a residue of ca. 50 g. This material was chromatographed on 350 g of silica gel with hexane–ethyl acetate as eluent (95:5 to 80:20), giving propiophenone (5), 11.4 g (30%), and (1*S*)-3-chloro-1-phenylpropan-1-ol (3): mp 60 °C (from hexane); $[\alpha]_D$ −23.9° (*c* 1, $CHCl_3$), 29.4 g (58%); ^1H NMR ($CDCl_3$), δ 2.00 (s br, 1 H, OH), 2.10 (m, 2 H, CH_2-2), 3.51 (m, 2 H, CH_2-3), 4.90 (dd, 1 H, CH-1, $J(1,2) = 5.0$, $J(1,2') = 7.0$ Hz), 7.2–7.4 (m, 5 H, C_6H_5). Anal. Calcd for $C_9H_{11}ClO$; C, 63.35; H, 6.49; Cl, 20.78. Found: C, 63.41; H, 6.44; Cl, 20.83.

[2-$^2H_2$]-3-Chloropropiophenone (8). Ethyl benzoylacetate (6), 48 g (0.25 mol), in 200 mL of dry tetrahydrofuran was refluxed under N_2 for 24 h with 30 mL of deuterium oxide and 18.5 mL (0.25 mol) of triethylamine. The reaction mixture was evaporated under vacuum and the residue was treated again under the same conditions with the same reagents. ^1H NMR of the residue: ($CDCl_3$) δ 1.27 (t, 3 H, CH_3, $J(CH_2,CH_3) = 7.0$ Hz), 3.98 (s, CH_2, 80% deuteration), 4.18 (q, 2 H, CH_2-O), 7.2–7.9 (m, 5 H, C_6H_5). The crude material in 100 mL of THF was added to 38 g (1 mol) of $LiAlH_4$ in 500 mL of boiling THF. After 24 h, sequential, treatment of the reaction mixture with ethyl acetate and a saturated solution of sodium and potassium tartrate and extraction with 3 × 200 mL of ethyl acetate afforded, after evaporation of the dried solution, 25 g of an oily residue. Chromatography of this material on 200 g of silica gel gave rise with 90:10 ethyl acetate–hexane to [2-$^2H_2$]-1-phenylpropane-1,3-diol (7): oil, 13 g (31%); ^1H NMR ($CDCl_3$) δ 1.88 (m, CH_2-2, 75% deuteration), 3.2 (br, 1 H, OH), 3.6 (br, 1 H, OH), 3.71 (s, 2 H, CH_2-3), 4.82 (s, 1 H, CH-1), 7.3 (s, 5 H, C_6H_5). Product 7, 11.5 g (75 mmol), in 80 mL of carbon tetrachloride was refluxed for 3 h under nitrogen with 19.8 g (75 mol) of triphenylphosphine. The solvent was evaporated under vacuum and the residue was chromatographed on 150 g of silica gel, obtaining with ethyl acetate–hexane (50:50) [2-$^2H_2$]-3-chloro-1-phenylpropan-1-ol, 11 g (85%). This material was treated in 100 mL of chloroform with 30 g of activated manganese dioxide under stirring for 60 h. The filtered solution was evaporated and the residue was chromatographed on 150 g of silica gel to give with hexane–ethyl acetate (80:20) [2-$^2H_2$]-3-chloropropiophenone (8) as an oil that solidified on standing, 8 g (73%): ^1H NMR ($CDCl_3$) δ 3.48 (m, CH_2-2, 75% deuteration), 3.91 (s, 2 H, CH_2-3), 7.25–8.0 (m, 5 H, C_6H_5).

Yeast Transformation of [2-$^2H_2$]-3-Chloropropiophenone (8). Product 8, 8 g (46 mmol), was treated with bakers' yeast as indicated above, but the reaction was interrupted after 4 h. During the transformation the pH ranged from 5.5 to 5. The residue obtained after the usual workup was separated by chromatography into a mixture of propiophenone and 3-chloropropiophenone, 3 g, and into (1*S*)-[2-$^2H_2$]-3-chloro-1-phenylpropan-1-ol (9), 3 g (38%): $[\alpha]_D$ −24° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.05 (s, 1 H, OH), 2.10 (m, CH_2-2, 75% deuteration), 3.52 (m, 2 H, CH_2-3), 4.90 (s, 1 H, CH-1), 7.2–7.4 (m, 5 H, C_6H_5). The mixture of propiophenone and 3-chloropropiophenone obtained above was submitted to bulb-to-bulb distillation at 30–40 mmHg (oven temp 80–100 °C). The distillate was submitted to a further distillation to provide 1.4 g of [2-^2H]-propiophenone (10), 1.4 g: ^1H NMR ($CDCl_3$) δ 1.22 (d, 3 H, CH_3, $J(H_2,CH_3) = 7.2$ Hz), 2.98 (qt, 1 H, H-2, $J(H_2,^2H_2) = 2.5$ Hz), 7.4–8.0 (m, 5 H, C_6H_5). The residue of the distillation, on silica gel chromatography, afforded [2-$^2H_2$]-3-chloropropiophenone (8), 0.7 g: ^1H NMR ($CDCl_3$) δ 2.05 (s, 1 H, OH), 2.10 (m, CH_2-2, 75% deuteration), 3.52 (m, 2 H, CH_2-3), 4.90 (s, 1 H, CH-1), 7.2–7.4 (m, 5 H, C_6H_5).

(1*R*,2*S*)-[2-^2H]-1-Phenylpropan-1-ol (13). (2*S*)-[2-^2H]-propiophenone (10), 1.2 g (8 mmol), in 10 mL of methanol was treated under stirring at −10 °C with sodium borohydride, 0.7 g (5.2 mmol). After 30 min the reaction mixture was diluted with 50 mL of ethyl acetate and the solution was washed twice with 25 mL of 2% HCl, dried, and evaporated. The oily residue, 1.2 g, was dissolved in 10 mL of dichloromethane and treated at 0 °C with 3 mL of acetic anhydride and 3 mL of pyridine. After 16 h the reaction mixture was poured into ice and the organic phase was separated and washed, in sequence, with 10 mL of 5% $NaHCO_3$, 10 mL of 3% HCl, and 10 mL of water. The residue obtained on evaporation of the solvent was chromatographed on 20 g of silica with hexane–ethyl acetate (85–15) to give (1*RS*,2*S*)-[2-^2H]-1-phenyl-1-acetoxypropane, 1 g (81%). This material, 0.9 g (5 mmol), in 80 mL of phosphate buffer, pH 7, was stirred at 23 °C in the presence of 200 mg of lipase SAM-2 (Fluka) for 16 h. Extractive workup and column chromatography of the residue gave with hexane–ethyl acetate (95:5) the acetyl derivative 12, 0.4 g: ^1H NMR (C_6D_6) δ 0.74 (d, 3 H, CH_3, $J(H\text{-}2,CH_3 = 7.2$ Hz), 1.66 (s, 3 H, $COCH_3$), 1.76 (m, H-2), 5.77 (d, 1 H, H-1, $J(H\text{-}1,H\text{-}2) = 7.2$ Hz); ^2H NMR (C_6H_6) δ 1.62 (^2H-2′) (65%), 1.76 (^2H-2) (35%). Further elution (80:20) gave the carbinol 13, 0.25 g, GLC analysis on Megadex 1 indicated 100% optical purity: ^1H NMR ($CDCl_3$) δ 0.91 (d, 3 H, CH_3, $J(H\text{-}2,CH_3) = 7.2$ Hz), 1.79 (br, 1 H, OH), 1.75 (m, H-2′), 4.57 (d, 1 H, H-1, $J(H\text{-}1,H\text{-}2') = 6.0$ Hz); ^2H NMR ($CHCl_3$) δ 1.82 (^2H-2) (92%), 1.76 (^2H-2′) (8%). Acetyl derivative: ^1H NMR (C_6D_6) δ 0.74 (d, 3 H, CH_3, $J(H\text{-}2,CH_3) = 7.2$ Hz), 1.67 (s, 3 H, $COCH_3$), 1.63 (m, H-2′), 5.77 (d, 1 H, $J(H\text{-}1,H\text{-}2') = 6.5$ Hz); ^2H NMR (C_6H_6) δ 1.61 (^2H-2′) (8%), 1.76 (^2H-2) (92%).

(1*R*,2*S*)-1-Phenylpropane-1,2-diol (15). Benzaldehyde (14) (80 g) in 50 mL of ethanol was added dropwise, under stirring, to a mixture of 1 kg of bakers' yeast and 1 kg of D-glucose in 5 L of tap water at 30 °C. A 16-h extractive workup, as indicated above, afforded an oily residue, yielding, on silica gel chromatography with hexane–ethyl acetate (from 85:15 to 15:85), benzyl alcohol and (1*R*,2*S*)-1-phenylpropane-1,2-diol (15), 14.3 g (20%): oil, $[\alpha]_D$ −38° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.03 (d, 3 H, CH_3, $J(2,CH_3) = 6.2$ Hz), 3.01 (s, br, 2 H, OH-1 and OH-2), 3.96 (qd, 1 H, CH-2, $J(1,2) = 4.4$ Hz), 4.64 (d, 1 H, CH-1), 7.20–7.35 (m, 5 H, C_6H_5). The dibenzoate of 15 showed $[\alpha]_D$ +60° (*c* 1, $CHCl_3$) (lit.[10b] for the 1*S*,2*R* enantiomer, −62.5°).

(1*R*,2*R*)-1-Phenyl-1,2-epoxypropane (17). (1*R*,2*S*)-1-Phenylpropane-1,2-diol (15), 15.2 g (100 mmol) in 100 mL of dichloromethane, containing 16 mL (200 mmol) of dry pyridine, was treated under stirring at 0 °C with 19 g (100 mmol) of 4-toluenesulfonyl chloride. After 16 h, the solution was poured into ice water and the separated organic phase was washed twice with 50 mL of cold 3% HCl and 25 mL of 5% sodium hydrogen carbonate, dried, and evaporated. The residue was rapidly passed through a short silica column with hexane–ethyl acetate (70:30) to give the 2-tosylate 16, 23 g (75%): oil, $[\alpha]_D$ −25.3° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.15 (d, 3 H, CH_3, $J(2,CH_3) = 6.7$ Hz), 2.35 (s, 1 H, OH-1), 2.44 (s, 3 H, CH_3-C_6H_4), 4.72 (qd, 1 H, CH-2, $J(1,2) = 3.3$ Hz), 4.90 (d, 1 H, CH-1), 7.20–7.80 (m, 9 H, C_6H_5 and C_6H_4). This material, 23 g (75 mmol), in 50 mL of methanol was treated with a solution of 4.5 g (83 mmol) of sodium methoxide in 100 mL of methanol at 0 °C. After 1 h the reaction mixture was poured in ice water and extracted with 2 × 200 mL of ethyl acetate.

The residue obtained upon evaporation of the dried organic phase was constituted by (1*R*,2*R*)-1-phenyl-1,2-epoxypropane (**17**), 9.5 g (90%): oil, $[\alpha]_D$ +47° (*c* 1, $CHCl_3$) (lit.[10b] +48°); ^1H NMR ($CDCl_3$) δ 1.44 (d, 3 H, CH_3), $J(2,CH_3)$ = 6.0 Hz), 3.03 (qd, 1 H, CH-2, $J(1,2)$ = 2.0 Hz), 3.57 (d, 1 H, CH-1), 7.20–7.40 (m, 5 H, C_6H_5).

(1*S*,2*R*)-[1-^{2}H]-1-Phenylpropan-2-ol (18) and (1*S*,2*S*)-[2-^{2}H]-1-Phenylpropan-1-ol (19). The epoxide **17**, 6 g (44 mmol), in 20 mL of THF was added under nitrogen to 2 g (44 mmol), of lithium aluminum deuteride in 70 mL of boiling THF. After 4 h, extractive workup and column chromatography afforded the alcohols **18** and **19**, in 9:1 mixture, 4.6 g (76%). GLC analysis on Megadex I indicates that **18** and **19** possess 0.95 and 0.92 ee, respectively: t_R(**18**) 30.66 min; t_R(*ent*-**18**) 31.11 min. t_R(*ent*-**19**) 35.56 min; t_R(**19**) 37.81 min. **18**: ^1H NMR ($CDCl_3$) δ 1.23 (d, 3 H, CH_3, $J(H\text{-}2,CH_3)$ 6.2 Hz), 1.70 (s, 1 H, OH), 2.68 (dt, 1 H, H-1, $J(H\text{-}1,H\text{-}2)$ = 7.9 Hz, $J(H\text{-}1,{}^2H\text{-}1')$ = 2.0 Hz), 4.00 (m, 1 H, H-2); ^2H NMR ($CHCl_3$) δ 2.76 (^2H-1′) (95%), 2.67 (^2H-1) (5%). **19**: ^1H NMR ($CDCl_3$) δ 0.90 (d, 3 H, CH_3), $J(H\text{-}2,CH_3)$ = 7.4 Hz), 1.70 (s, 1 H, OH), 1.80 (dqt, 1 H, H-2, $J(H\text{-}1,H\text{-}2)$ = 7.2 Hz, $J(H\text{-}2,{}^2H\text{-}2')$ = 2.0 Hz), 4.57 (d, 1 H, H-1); ^2H NMR ($CHCl_3$) δ 1.8 (^2H-2) (10%), 1.77 (^2H-2′) (90%). Acetyl derivative of **18**: ^1H NMR (C_6D_6) δ 1.03 (d, 3 H, CH_3, $J(H\text{-}2,CH_3)$ = 6.0 Hz), 1.64 (s, 3 H, $COCH_3$), 2.76 (dt, 1 H, H-1, $J(H\text{-}1,H\text{-}2)$ = 6.5 Hz, $J(H\text{-}1,{}^2H\text{-}1')$ = 2.0 Hz), 5.16 (m, 1 H, H-2); ^2H NMR (C_6H_6) δ 2.48 (^2H-1′) (95%), 2.75 (^2H-1) (5%). Acetyl derivative of **19**: ^1H NMR (C_6D_6) δ 0.73 (d, 3, CH_3, $J(H\text{-}2,CH_3)$ = 7.2 Hz), 1.67 (s, 3 H, $COCH_3$), 1.77 (m, H-2, partially overlapped with acetyl signals), 5.77 (d, 1 H, H-1, $J(H\text{-}1,H\text{-}2)$ = 7.2 Hz); ^2H NMR (C_6H_6) δ 1.62 (^2H-2′) (90%), 1.77 (^2H-2) (10%).

(2*S*)-1-Phenylpropan-2-ol (23) and (2*S*)-1-[3-(Trifluoromethyl)phenyl]propan-2-ol (24). The yeast reduction of the two ketones **21** and **22** was performed, as indicated above, with a ketone/yeast ratio of 70 g/kg. Carbinol **23** was shown to be enantiomerically pure by GLC chiral column chromatography and comparison with an authentic sample. Product **24**, an oil, $[\alpha]_D$ +24.9° (*c* 1, ethanol), was isolated in 85–90% yield by extraction and vacuum distillation: ^1H NMR ($CDCl_3$) δ 1.22 (d, 3 H, CH_3, $J(H\text{-}2,CH_3)$ = 6.0 Hz), 1.55 (s, 1 H, OH), 2.77 (d, 2 H, H-1 and H-1′, $J(H\text{-}1,H\text{-}2)$ = $J(H\text{-}1',H\text{-}2)$ = 6.2 Hz), 4.02 (tq, 1 H, H-2), 7.3–7.55 (m, 4 H, C_6H_4). Anal. Calcd for $C_{10}H_{11}OF_3$: C, 58.83; H, 5.42. Found: C, 58.61; H, 5.36. Product **24** was converted into the ester with (+)-MTPA upon treatment with (+)-MTPA chloride in pyridine. Comparison of the ^1H NMR spectrum of this material with that of the racemic alcohol indicated the enantiomeric purity of **24**. Ester of racemic **24** with (+)-MTPA: ^1H NMR ($CDCl_3$) δ 1.34 (d, 3 H, CH_3, $J(H\text{-}2,CH_3)$ = 6.0 Hz), 1.39 (d, 3 H, CH_3, $J(H\text{-}2,CH_3)$ = 6.2 Hz), 2.83–3.06 (m, 4 H, H-1 and H-1′), 3.34 (s, 3 H, OCH_3), 3.43 (s, 3 H, OCH_3), 5.41 (m, 2 H, H-2), 7.2–7.5 (m, 9 H, C_6H_5 and C_6H_4). Ester of **24** with (+)-MTPA: ^1H NMR ($CDCl_3$) δ 1.39 (d, 3 H, CH_3, $J(H\text{-}2,CH_3)$ = 6.2 Hz, 2.90 (dd, 1 H, $J(H\text{-}1,H\text{-}1')$ = 14.0 Hz, $J(H\text{-}1,H\text{-}2)$ = 5.5 Hz, 2.98 (dd, 1 H, H-1′, $J(H\text{-}1',H\text{-}2)$ = 7.5 Hz), 3.43 (s, 3 H, OCH_3), 5.42 (m, 1 H, H-2), 7.2–7.5 (m, 9 H, C_6H_5 and C_6H_4).

(2*R*)-2-(Ethylamino)-1-[3-(trifluoromethyl)phenyl]propane (29) (*l*-Fenfluramine). The alcohol **24**, 51 g (250 mmol), in 250 mL of dry pyridine was treated at 0 °C with 85 g (500 mmol) of 4-toluenesulfonyl chloride. After 16 h the reaction mixture was poured into ice water and extracted with 3 × 200 mL of dichloromethane. The organic phase, washed with 2 × 100 mL of cold 3% HCl, 100 mL of 5% sodium hydrogen carbonate, and water, once evaporated, gave tosylate **25**, 81 g (90%), as an unstable oil: $[\alpha]_D$ +25.74° (*c* 1, ethanol). This material, 81 g (220 mmol), in 500 mL of 60% aqueous dimethylformamide was refluxed for 5 h with 65 g (500 mmol) of sodium azide. The cold reaction mixture was extracted four times with 300 mL of a 1:1 mixture of hexane–ethyl acetate. The organic phase was washed five times with 300 mL of water, dried, and evaporated. The oily residue was chromatographed on 400 g of silica gel, eluting with hexane–ethyl acetate (80:20) the azide **27**, 42 g (84%): $[\alpha]_D$ −32.2° (*c* 1, ethanol); ^1H NMR ($CDCl_3$) δ 1.35 (d, 3 H, CH_3, $J(H\text{-}2,CH_3)$ = 6.3 Hz), 2.92 (dd, 1 H, H-1, $J(H\text{-}1,H\text{-}1')$ = 14.1, $J(H\text{-}1,H\text{-}2)$ = 6.0 Hz), 3.02 (dd, 1 H, H-1′, $J(H\text{-}1',H\text{-}2)$ = 6.0 Hz), 3.32 (ddq, 1 H, H-2), 7.3–7.6 (m, 4 H, C_6H_4). Anal. Calcd for $C_{10}H_{10}N_3F_3$: C, 52.64; H, 4.41; N, 18.40. Found: C, 52.58; H, 4.38; N, 18.51. The azide **27**, 22.8 g (100 mmol), in 150 mL of absolute ethanol was hydrogenated in a Parr apparatus at room temperature at 2 atm hydrogen in the presence of 500 mg of 10% Pd/C. To the filtered solution were added acetaldehyde, 4.4 g (110 mmol), and, after 3 h, sodium borohydride, 0.5 g (178 mmol), in small portions, under stirring at 0 °C. The reaction mixture was concentrated to a small volume, under vacuum, diluted with water, and extracted with 2 × 100 mL of diethyl ether. The residue obtained upon evaporation of the solvent was distilled at 120 °C at 0.1 mmHg to give **29**, 19 g (82%): ^1H NMR ($CDCl_3$) δ 1.35 (d, 3 H, CH_3, $J(H\text{-}2,CH_3)$ = 6.3 Hz), 1.57 (t, 3 H, CH_2CH_3, $J(CH_2,CH_3)$ = 7.0 Hz), 2.97 (dd, 1 H, H-1, $J(H\text{-}1,H\text{-}1')$ = 13.0 Hz, $J(H\text{-}1,H\text{-}2)$ = 11.0 Hz), 3.09 (dq, 1 H, NC*H*H′-, $J(H,H')$ = 12.3 Hz), 3.17 (dq, 1 H, NCH*H*′-), 3.41 (ddq, 1 H, H-2, $J(H\text{-}1',H\text{-}2)$ = 3.5 Hz), 3.67 (dd, 1 H, H-1′), 7.35–7.60 (m, 4 H, C_6H_4). Anal. Calcd for $C_{11}H_{16}NF_3$: C, 62.33; H, 6.96; N, 6.05. Found: C, 62.17; H, 6.91; N, 6.01. Due to the low specific optical rotations of optically pure fenfluramine and of its hydrochloride, the absolute configuration and optical purity of the present sample were determined by GLC analysis of the amide with (*S*)-*N*-(trifluoroacetyl)proline,[16] obtained by treating the dichloromethane solution of the amine with (*S*)-*N*-(trifluoroacetyl)prolyl chloride and comparison with authentic samples. Analysis conditions: 25 m × 0.25 i.d., liquid silicone film, column temperature 220 °C, hydrogen carrier gas. t_R(*R* enantiomer), 9.6 min; t_R(*S* enantiomer): 10.27 min. The fenfluramine sample had the *R* configuration depicted in **29**, with 0.97 ee. (*S*)-Fenfluramine (**26**) was obtained as follows. The tosylate **25**, 55 g (150 mmol) in 150 mL of dry dimethylformamide, was refluxed 6 h with sodium benzoate, 43.2 g (300 mmol). The reaction mixture was poured into ice water and extracted with 3 × 200 mL of hexane–ethyl acetate (1:1). The organic extract was washed with 5 × 200 mL of water and evaporated, and the residue was treated with 500 mL of boiling 2 N NaOH for 5 h. The cold reaction mixture was extracted with 2 × 200 mL of diethyl ether to give, once evaporated, the 2*R* alcohol **30**, 25 g (81%) after vacuum distillation: $[\alpha]_D$ −23.2° (*c* 1, ethanol). From **30**, (*S*)-fenfluramine (**26**), 0.9 ee, was obtained in ca. 60% overall yield.

(*R*)-Fluoxetine (31). (1*S*)-3-Chloro-1-phenylpropan-1-ol (**3**), obtained by yeast reduction of **2**, was treated with trifluorocresol in THF in the presence of triphenylphosphine and diethyl azodicarboxylate at room temperature to give (3*R*)-1-chloro-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propane, in 55% yield after column chromatography purification. The latter, upon treatment with methylamine, yielded (*R*)-fluoxetine (**31**) (75%). **31**·HCl: $[\alpha]_D$ −13.6° (*c* 1, $CHCl_3$) in agreement with literature values ($[\alpha]_D$ −13.8° (*c* 1, $CHCl_3$)).[1-3]

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Supplementary Material Available: Spectra of compounds **8**, **9**, **12**, **13**, **15**, **18** + **19**, and acetyl derivatives of **18** + **19** (7 pages). Ordering information is given on any current masthead page.

(16) Beckett, A. H.; Testa, B. *J. Chromatogr.* **1972**, *69*, 285.