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Stereochemistry of the Conversion of 2-Phenoxyethanol into Phenol and Acetaldehyde by *Acetobacterium* sp.

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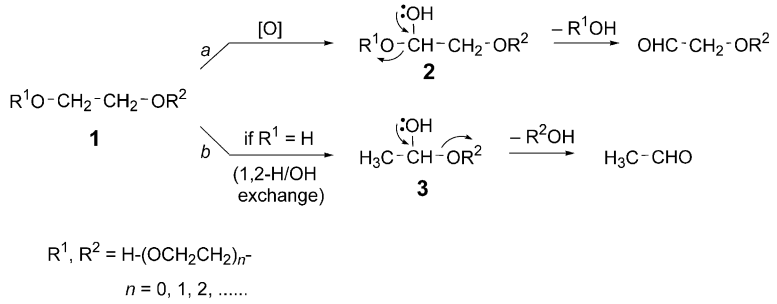
The conversion of 2-phenoxyethanol to phenol and acetate by the anaerobic bacterium *Acetobacterium* sp. strain LuPhet1 proceeds through acetaldehyde with concomitant migration of a H-atom from C(1) to C(2) of the glycolic moiety. Separate feeding experiments with (*R*)- and (*S*)-2-phenoxy(1-^{2}H)ethanol, prepared *via* chemoenzymatic syntheses, indicate that the H-atom involved in the 1,2-shift is the *pro-S* one of the enantiotopic couple of the alcohol function.

Introduction. – Ether cleavage is particularly difficult both *in vitro* [1] and *in vivo* [2]. For microbial degradation of polyethylene glycol (PEG) molecules (**1**) both by aerobic [3] and anaerobic [4] bacteria, several different biochemical mechanisms have been proposed. However, the formation of a hemi-acetal structure (*i.e.*, **2** and **3**) as the penultimate step of the ether cleavage appears to be the predominant strategy [2] (*Scheme 1*).

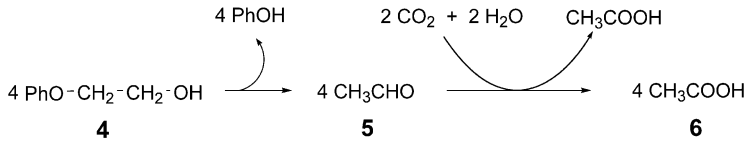
Scheme 1. *Putative Reaction Mechanisms of Microbial PEG Degradation under Aerobic* (*a*) [3] *and Anaerobic* (*b*) [4f] *Conditions*



The anaerobic homoacetogenic *Acetobacterium* strain LuPhet1 was found to degrade low-molecular-weight PEGs, but also to convert 2-phenoxyethanol (**4**) *via* MeCHO (**5**) to acetate **6** with release of phenol (*Scheme 2*) [4f]. Thus, **4** can be regarded as a useful model compound to study the enzymatic ether cleavage of PEG.

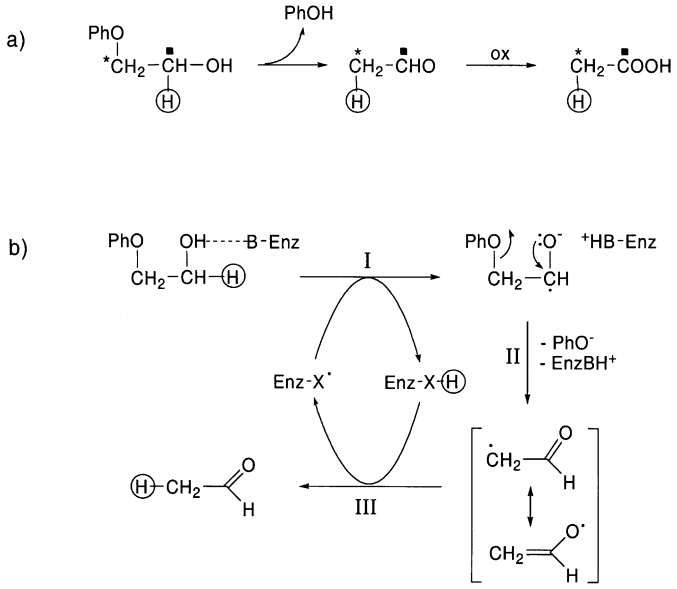
Experiments carried out with ^{2}H- and ^{13}C-labeled 2-phenoxyethanol and resting cell suspensions of strain LuPhet1 allowed us to clarify the fate of the C- and H-atoms of **4** in the reaction giving rise to MeCHO (isolated as AcONa). As shown in *Scheme 3*,*a*,

Scheme 2. *Stoichiometry of the Anaerobic Fermentation of 2-Phenoxyethanol by* Acetobacterium *sp. Strain LuPhet1*



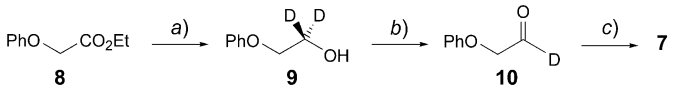
the alcohol function of 2-phenoxyethanol becomes a carboxy group, whereas the adjacent CH_2 group is transformed into a Me group with concomitant *intramolecular* 1,2-H shift [5]. These findings could be interpreted in terms of 1,2-PhO shift as a route alternative to the 1,2-OH shift previously hypothesized (see path *b* of *Scheme 1*, where $R^2 = Ph$) [4f]. However, the radical mechanism depicted in *Scheme 3,b* [5], which does not involve a hemi-acetal as a necessary intermediate, seems more likely. It is supported by the well-recognized propensity of ketyl radicals (radical anions) to eliminate adjacent leaving groups [6] (step *II* in *Scheme 3,b*). In addition, it is consistent with a H-transfer without exchange with the medium [7], and, in this respect, it is reminiscent of diol-dehydratase-catalyzed reactions [8]. We report here the determination of a cryptostereochemical feature of the transformation of 2-phenoxyethanol (**4**) into MeCHO, namely, the enantioselectivity exerted by the enzyme in the H-abstraction from the substrate (*e.g.*, reaction *I* in *Scheme 3,b*).

Scheme 3. a) *Fate of H- and C-Atoms in the Conversion of 2-Phenoxyethanol to AcOH by Strain LuPhet1*. b) *Hypothetical Enzymatic Mechanism for Glycol Ether Cleavage* [5].



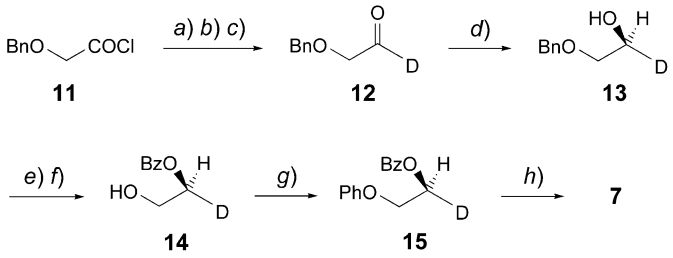
Results and Discussion. – To distinguish between the enantiotopic H-atoms of the primary alcohol group of **4**, we prepared both the *C*(1)-monodeuterated enantiomers of 2-phenoxyethanol, *i.e.*, **7** and *ent*-**7**. A substantial amount of (*S*)-2-phenoxy(1-^{2}H)ethanol (**7**) was synthesized by baker's yeast mediated hydrogenation of the corresponding deuterated aldehyde **10**, which was prepared from ethyl 2-phenoxyacetate (**8**) *via* the dideuterated alcohol (**9**; *Scheme 4*). The enantiomeric purity (*ca.* 100%) and the D content (monodeuterated molecules $>98\%$) of the alcohol resulting from the enzymatic reduction were checked by ^{1}H-NMR of the *Mosher* ester [9] (compared with the ester of the racemic mixture, *Fig. 1*,*a* and *b*) and by MS measurements. The configuration of **7** was expected to be (*S*) on the basis of the well-known empirical rules regarding the stereoselective hydrogenation of the carbonyl group by *Saccharomyces cerevisiae* (baker's yeast) [10]. In any case, it was confirmed by chemical correlation of **7** with (+)-(*S*)-2-(benzyloxy)(1-^{2}H)ethanol (**13**) [11] (*Scheme 5*). Compound **13** was obtained through the baker's yeast mediated reduction of the deuterated aldehyde **12** and was shown to be identical in all respects (including the sign and the value of optical rotation) with the compound of unequivocal configuration previously synthesized by an independent route [11]. The conversion of **13** to **7** was then achieved by exploiting the activation of the alcohol **14** with the *Mitsunobu* reagents [12], followed by reaction with phenol to give **15**. The inversion of

Scheme 4



a) $LiAlD_4$, Et_2O. *b*) *Swern* oxidation. *c*) Bakers's yeast.

Scheme 5



a) EtOH, Py, CH_2Cl_2. *b*) $LiAlD_4$, Et_2O. *c*) *Swern* oxidation. *d*) Baker's yeast. *e*) PhCOCl, Py, CH_2Cl_2. *f*) H_2, 10% Pd/C, MeOH. *g*) PPh_3, diisopropyl azodicarboxylate (DIAD), PhOH, THF. *h*) NaOH, EtOH.

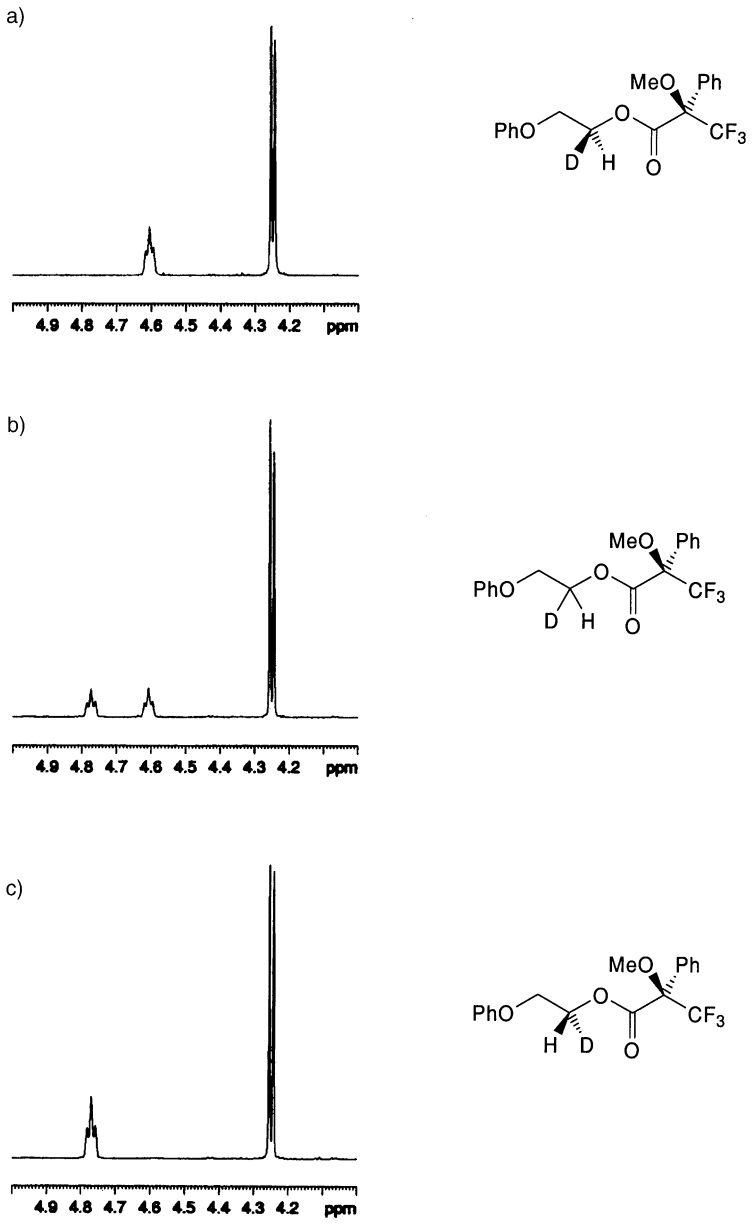


Fig. 1. *^{1}H-NMR Signals* (300 MHz, $CDCl_3$) *due to the glycolic moiety of* Mosher's *(*R*)-esters of* a) *(*S*)-2-phenoxy(1-^{2}H)ethanol*; b) rac-*2-phenoxy(1-^{2}H)ethanol, and* c) *(*R*)-2-phenoxy(1-^{2}H)ethanol*

the configuration at C(1) of (*S*)-2-phenoxy(1-^{2}H)ethanol (**7**) was accomplished by means of the classical *Mitsunobu* procedure [12], thus providing enantiomerically pure *ent*-**7** in good yields (*cf.* the *Mosher* ester in *Fig. 1,c*).

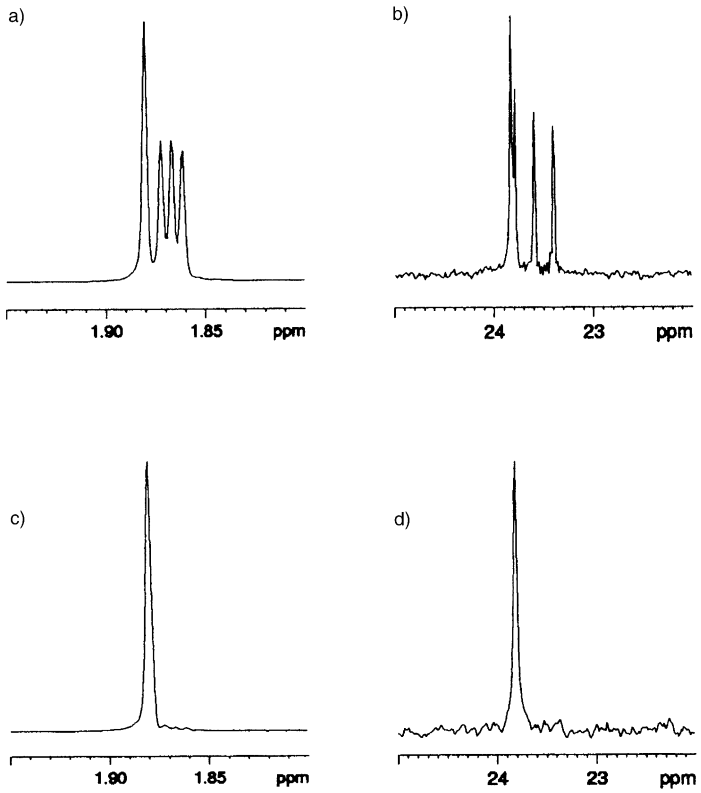


Fig. 2. *^{1}H- (400 MHz) and ^{13}C-NMR (100 MHz) spectra of AcONa* (in $NaOD/D_2O$; Me-group resonances only) *obtained by fermentation of (*S*)-2-phenoxy(1-^{2}H)ethanol* (*a* and *b*) *and (*R*)-2-phenoxy(1-^{2}H)ethanol* (*c* and *d*). For values of coupling constants and isotope shifts, see text.

When *Acetobacterium* cells (strain LuPhet1) [5] were fed with (*S*)-2-phenoxy(1-^{2}H)ethanol (**7**), the resulting sodium acetate was found to be a mixture of monodeuterated and nondeuterated molecules in a ratio[1]) of *ca.* 2.5 : 1. In fact, the ^{1}H- and ^{13}C-NMR spectra of this acetate exhibited the typical patterns of signals due to CH_2D (1 : 1 : 1 *triplet*, $^{2}J(H,D) = 2.05$ Hz) and $^{13}CH_2D$ (1 : 1 : 1 *triplet*, $J(C,D) = 19.52$ Hz). These *triplets* were upfield to the *singlets* ($\delta(H) = 1.867$ ppm, $^{2}\Delta H(D) = 13.9$ ppb; $\delta(C) = 23.593$ ppm, $\Delta C(D) = 0.235$ ppm) due to the nondeuterated Me group (*Fig. 2,a* and *b*) [5]. By contrast, the ^{1}H- and ^{13}C-NMR spectra of sodium acetate obtained from fermentation of (*R*)-2-phenoxy(1-^{2}H)ethanol (*ent*-**7**) showed only the signals of the CH_3 and $^{13}CH_3$, respectively, in the Me-group region (*Fig. 2,c* and *d*). The combined results of these feeding experiments were clearly indicative of the capacity of the enzyme to discriminate between the two H-atoms at C(1) of **4**, with consequent

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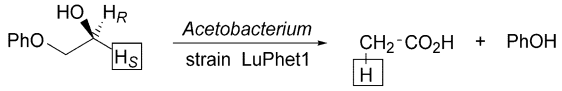
[1]) As calculated from the integrated peak areas in the ^{1}H-NMR spectra, taking into account the number of H-atoms in the two species.

migration of the (*pro-S*) one. It can be noted that, in the acetate arising from the fermentation of **7**, some nondeuterated molecules are present besides the monodeuterated ones[1]). This fact is not due to a partial exchange of the mobile H-atom with the medium [5], but can be explained by considering that additional $CH_3CO_2^-$ is produced by CO_2 reduction by this homoacetogenic bacterium (*cf. Scheme 2*) [4f][5].

In conclusion, the ether cleavage in the biodegradation of 2-phenoxyethanol (**4**) brings about the specific 1,2-shift of one of the two enantiotopic H-atoms at C(1), as depicted in *Scheme 6*.

Scheme 6. *Stereospecificity of the Microbial Conversion of 2-Phenoxyethanol to AcOH and PhOH*



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Experimental Part

General. TLC: Silica gel *60 F_{254}*-precoated aluminum sheets (*Merck*); detection either by UV or spraying with a ceric sulfate/ammonium molybdate soln., followed by heating to *ca.* 150°; eluent, petroleum ether/AcOEt 5:2. Flash chromatography (FC): silica gel (40–63 μm; *Merck*); eluent, petroleum ether/AcOEt 5:2, unless stated otherwise. GC: *Dani 3850* gas chromatograph; injector, 220°; detector (FID), 220°; home-made 2 m × 2 mm i.d. glass column, 5% *FFAP* on *Chromosorb W,* 80–100 mesh, isothermal analysis at 200°; t_R in min. Optical rotations: *Perkin-Elmer 241* polarimeter; 1-dm cell. NMR Spectra: *Bruker AC-300* spectrometer at 300.13 (^{1}H), 46.07 (^{2}H), and 75.47 MHz (^{13}C), and *Bruker Avance-400* spectrometer at 400.13 (^{1}H) and 100.61 MHz (^{13}C); δ in ppm *vs.* solvent as internal reference (C(H)DCl_3: δ(H/D) 7.25, δ(C) 77.00) or sodium 3-(trimethylsilyl)(2,2,3,3-$^2H_4$)propanoate (δ(Me) = 0 ppm) in the case of D_2O/NaOD (pH > 10); *J* in Hz; ^{13}C multiplicities from APT spectra. EI-MS (*m*/*z* [%]): *VG 7070 EQ* mass spectrometer; at 70 eV.

Fermentation Experiments and *Isolation of Sodium Acetate.* Labelled 2-phenoxyethanol samples were transformed by dense cell suspensions of *Acetobacterium* sp. strain LuPhet1 [5], and the produced acetate was extracted and prepared as described in [5].

Data of Sodium Acetate. ^{1}H-NMR (400 MHz, D_2O/NaOD): 1.8670 (*t*, ^2J(H,D) = 2.05, C*H*$_2$D); 1.8809 (*s*, CH_3). ^{13}C-NMR (100 MHz, D_2O/NaOD): 23.593 (*t*, *J*(C,D) = 19.52, CH_2D); 23.828 (*s*, CH_3); 181.975 (COO).

*(*S*)-2-Phenoxy(1-^{2}H)ethanol* (**7**). A stirred soln. of oxalyl chloride (1.7 ml, 19.7 mmol) in dry CH_2Cl_2 (60 ml) was cooled to −80° under N_2 and treated dropwise with DMSO (2.8 ml, 39.4 mmol), keeping the temp. below −65°. After 15 min, a soln. of *2-phenoxy(1,1-$^2H_2$)ethanol* (**9**; 1.4 g, 10 mmol), prepared from ethyl *2-phenoxyacetate* (**8**) by a published procedure [5], in dry CH_2Cl_2 (15 ml) was added over a period of 5 min. Stirring was continued at −65° for 15 min, then Et_3N (6.9 ml, 49.5 mmol) was added dropwise with stirring. After 10 min, the cooling bath was removed, and the mixture was stirred for 2 h at r.t. H_2O (10 ml) was added, stirring was continued for 10 min, and the two layers were separated. The aq. phase was extracted with CH_2Cl_2 (2 × 10 ml), and the org. layers were combined, washed two times with brine, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave the crude *2-phenoxy(1-^{2}H)acetaldehyde* (**10**; 1.35 g, quant. yield) as an oil, which was used immediately in the next step. TLC: R_f 0.35. GC: t_R 2.4. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.59 (*s*, PhOC*H*$_2$); 6.87–7.11 (*m*, 3 arom. H); 7.30–7.41 (*m*, 2 arom. H). ^{2}H-NMR ($CHCl_3$): 9.89 (br. *s*, ^{2}H–C(1)). Compound **10** (675 mg, 4.9 mmol), dissolved in 7 ml of EtOH, was gradually added to a suspension of baker's yeast (500 g) in preboiled distilled water (500 ml), and the mixture was vigorously stirred at 37° for 24 h (GC and TLC control). The fermentation broth was saturated with NaCl and continuously extracted with Et_2O. The Et_2O extract was dried (Na_2SO_4), evaporated under reduced pressure, and purified by FC to give pure **7** (400 mg, 58%). TLC: R_f 0.19. GC: t_R 4.6. $[\alpha]_D^{25} = +0.394$ (*c* = 9.4, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 2.26 (br. *s*, OH); 3.92 (*tt*, *J* = 4.6, 1.8, H–C(1)); 4.05 (*d*, *J* = 4.6, CH_2); 6.89–6.97 (*m*, 3 arom. H); 7.24–7.30 (*m*, 2 arom.

H). ^{2}H-NMR ($CHCl_3$): 3.91 (br. *s*, ^{2}H–C(1)). ^{13}C NMR (100 MHz, $CDCl_3$): 61.06 (*t*, ^1J(C,D) = 21.9, C(1)); 69.01 (CH_2); 114.52, 121.07, 129.48 (arom. CH); 158.57 (arom. C). EI-MS: 139 (40, M^+), 122 (3), 107 (10), 94 (100); ($^2H_1$) species > 98%. ee was found to be higher than 99% as shown by the NMR spectrum of its (*R*)-MTPA ester (see below and *Fig. 1,a*).

*(*R*)-2-Phenoxy(1-^{2}H)ethanol* (*ent*-**7**). PPh_3 (1.65 g, 6.3 mmol), 4-nitrobenzoic acid (1.05 g, 6.3 mmol) and **7** (294 mg, 2.1 mmol) were dissolved in dry THF/toluene 1:1 (30 ml) under N_2. The soln. was cooled to −20°, and diisopropyl azodicarboxylate (DIAD; 1.24 ml, 6.3 mmol) was added dropwise with stirring over a 5-min period. After 10 min, the reaction was complete (TLC and GC analysis). Removal of the solvent under reduced pressure gave a residue, which was dissolved in hexane/AcOEt 2:1 and cooled to 0°. Insoluble material was removed by filtration, the filtrate was evaporated under reduced pressure, and the residue was purified by FC to give pure 2-phenoxy(1-^{2}H)ethyl 4-nitrobenzoate (505 mg, 83%). TLC: R_f 0.49. GC: t_R 5.3. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.33 (*d*, *J* = 4.5, CH_2); 4.69 (br. *t*, *J* = 4.5, H–C(1)); 6.92–7.00 (*m*, 3 arom. H); 7.24–7.32 (*m*, 2 arom. H); 8.19–8.41 (*m*, 4 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 61.78 (*t*, ^1J(C,D) = 22.1, C(1)); 63.45 (CH_2); 112.49, 121.28, 121.91, 128.62, 129.48 (arom. CH); 133.06, 148.43, 156.23 (arom. C); 162.46 (COO).

To a soln. of the above 2-phenoxy(1-^{2}H)ethyl 4-nitrobenzoate (500 mg, 1.73 mmol) in THF (10 ml) was added 2N NaOH (3 ml). After vigorous stirring for 2 h at r.t., the mixture was diluted with Et_2O and H_2O, the two phases were separated, and the aq. layer was extracted with Et_2O. The combined org. extract was dried (Na_2SO_4), concentrated, and the residue was purified by FC (petroleum ether/AcOEt 1:1) to give *ent*-**7** (211 mg, 88%). Data as for **7**, except for optical rotation: $[\alpha]_D^{25} = -0.372$ (*c* = 11.0, $CHCl_3$). Enantiomeric purity (ee > 99%) was checked by ^{1}H-NMR spectrum of its (*R*)-MTPA ester (see below and *Fig. 1,c*).

rac-*2-Phenoxy(1-^{2}H)ethanol*. H_2O (1 ml) and *Amberlyst-15* (300 mg) were added to a soln. of commercial 2-phenoxyacetaldehyde dimethyl acetal (250 mg, 1.37 mmol) in MeCN (10 ml), and the mixture was kept at r.t. under stirring. After 8 h, the resin was filtered off, and the solvent was evaporated under reduced pressure to give crude 2-phenoxyacetaldehyde (180 mg, 96%) [13]. TLC: R_f 0.35. GC: t_R 2.4. It was dissolved in EtOH (15 ml), cooled to 0° and treated portionwise with $NaBD_4$ (35 mg, 0.8 mmol) under stirring. The mixture was allowed to warm to r.t. and stirred for additional 2 h. Usual workup and purification by FC (petroleum ether/AcOEt 1:1) gave pure *rac*-2-phenoxy(1-^{2}H)ethanol. Data as for **7**.

Preparation of MTPA (=3,3,3-Trifluoro-2-methoxy-2-phenylpropanoic Acid) Esters. The (*R*)-MTPA esters of **7**, *ent*-**7**, and *rac*-2-phenoxy(1-^{2}H)ethanol were prepared from commercially available (+)-(*S*)-MTPA-Cl according to a published procedure [9]. Usually, 15 mg of the alcohol was used.

*(*R*)-MTPA Ester of* **7**: TLC: R_f 0.54. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.59 (*s*, MeO); 4.25 (*d*, *J* = 4.8, $PhOCH_2$); 4.61 (br. *t*, *J* = 4.8, C*H*^{2}HOCO); 6.88–6.91 (*m*, 2 arom. H); 7.02 (*t*, *J* = 7.2, 1 arom. H); 7.28–7.42 (*m*, 5 arom. H); 7.56–7.61 (*m*, 2 arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.90 (MeO); 64.42 (*t*, ^1J(C,D) = 23.6, *C*H^{2}HOCO); 65.57 (CH_2); 115.00, 121.80, 127.74, 128.81, 129.97 (arom. CH); 123.66 (*q*, ^1J(C,F) = 288.9); 132.57, 158.57 (arom. C); 166.96 (COO) (see *Fig. 1,a*).

*(*R*)-MTPA Ester of* ent-**7**: ^{1}H-NMR (400 MHz, $CDCl_3$): 4.77 (br. *t*, *J* = 4.8, C*H*^{2}HOCO) (see *Fig. 1,c*).

*(*R*)-MTPA Ester of* rac-*2-Phenoxy(1-^{2}H)ethanol:* ^{1}H-NMR (300 MHz, $CDCl_3$): 4.61 (br. *t*, *J* = 4.8), 4.77 (br. *t*, *J* = 4.8) (C*H*^{2}HOCO) (see *Fig. 1,b*).

*Preparation of (+)-(*S*)-2-(Benzyloxy)(1-^{2}H)ethanol* (**13**). 2-(Benzyloxy)(1-^{2}H)acetaldehyde (**12**) [11], prepared from commercial *2-benzyloxyacetyl chloride* (**11**) according to published procedures [5][11], was submitted to baker's yeast reduction under the conditions described above for compound **7**, giving rise to an oil, which was purified by FC to afford **13** [11] (51% overall yield) in pure form. TLC: R_f 0.15. GC: t_R 4.8. $[\alpha]_D^{25} = +0.301$ (*c* = 80, $CHCl_3$; [11]: $[\alpha]_D^{20} = +0.387$ (neat)). ^{1}H-NMR: as in [11]. ^{13}C-NMR (75 MHz, $CDCl_3$): 61.51 (*t*, ^1J(C,D) = 21.7, C(1)); 71.40, 73.30 (2 CH_2); 127.78, 128.47 (arom. CH); 138.00 (arom. C).

Conversion of **13** *into* **7**. Compound **13** was converted to (*S*)-2-benzyloxy(1-^{2}H)ethyl benzoate in 90% yield as reported in [11]. This ester (2.1 g, 8.2 mmol) was hydrogenated over 10% Pd/C (1 g) in MeOH (40 ml) at r.t. for 3 h. Filtration of the catalyst and removal of the solvent under reduced pressure gave *(*S*)-2-hydroxy(1-^{2}H)ethyl benzoate* (**14**; 1.3 g, 95%). TLC: R_f 0.36. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.93 (br. *s*, OH); 3.88 (*d*, *J* = 4.7, CH_2); 4.37 (br. *t*, *J* = 4.7, H–C(1)); 7.34–7.52 (*m*, 3 arom. H); 7.98–8.02 (*m*, 2 arom. H). ^{13}C NMR (75 MHz, $CDCl_3$): 61.11 (CH_2); 66.31 (*t*, ^1J(C,D) = 22.8, C(1)); 128.37, 129.67, 133.15 (arom. CH); 129.84 (arom. C); 167.00 (COO).

A stirred soln. of PPh_3 (1.47 g, 5.6 mmol) and diisopropyl azodicarboxylate (DIAD; 1.1 ml, 5.6 mmol) in THF (60 ml) at 0° was treated, sequentially, with a soln. of freshly distilled PhOH (790 mg, 8.4 mmol) in THF (4 ml) and then with a soln. of **14** (600 mg, 3.6 mmol) in THF (4 ml) over a period of 15 min. The mixture was allowed to warm to r.t. and was stirred for an additional 1 h (TLC control). After addition of H_2O (3 ml) and a few drops of conc. HCl, the solvent was removed under reduced pressure. The residue was dissolved in Et_2O

(40 ml), washed with 2N NaOH and with H_2O, dried (Na_2SO_4), and concentrated to *ca.* a half volume under reduced pressure. Insoluble materials were removed by filtration, the filtrate was evaporated under reduced pressure, and the residue was purified by FC to give pure *(S)-2-phenoxy(1-^{2}H)ethyl benzoate* (**15**) (600 mg, 68%). TLC: R_f 0.49. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.31 (*d*, *J* = 4.8, CH_2); 4.66 (br. *t*, *J* = 4.8, C*H*^{2}H); 6.95–7.01 (*m*, 3 arom. H); 7.25–7.59 (*m*, 5 arom. H); 8.05–8.10 (*m*, 2 arom. H). ^{13}C NMR (75 MHz, $CDCl_3$): 63.09 (*t*, ^1J(C,D) = 23.0, CH^{2}H); 65.97 (CH_2); 114.78, 121.22, 128.36, 129.56, 129.74, 133.07 (arom. CH); 130.02, 158.63 (arom. C); 166.50 (COO).

NaOH in pellets (2.0 g) was added to a soln. of **15** (400 mg, 1.6 mmol) in EtOH (50 ml), and the mixture was refluxed for 1 h. After cooling to r.t., the solvent was evaporated, and the residue was dissolved in Et_2O/H_2O 1:1 (40 ml) with stirring. The two layers were separated, and the aq. phase was extracted with Et_2O. The org. phases were combined, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by passing through a short column of silica gel (petroleum ether/AcOEt 1:1), to give (*S*)-2-phenoxy(1-^{2}H)ethanol (210 mg, 92%), which was found to be identical to **7** according to the ^{1}H- and ^{13}C-NMR, MS, and optical rotation data.

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