214. Preparation by Yeast Reduction and Determination of the Sense of Chirality of Enantiomerically Pure Ethyl (−)-4,4,4-Trichloro-3-hydroxy- and (+)-4,4,4-Trifluoro-3-hydroxybutanoate

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Summary

Reduction of ethyl 4,4,4-trichloro- and 4,4,4-trifluoro-3-oxobutanoate by fermenting baker's yeast *(Saccharomyces cerevisiae)* on a preparative scale (20–50 g in *ca.* 3 l of H_2O) gave 70–80% yields of the trichloro- [(−)-(*S*)-**1a**] and trifluoro-hydroxyesters [(+)-(*R*)-**2a**] of *ca.* 85 and 45% ee, respectively. Both, (−)-**1a** and (+)-**2a** could be obtained in > 98% ee by subsequent crystallization (of (−)-**1a**, (+)-**2a** or the 3,5-dinitrobenzoate (+)-**2b**). The absolute configuration of both hydroxyesters was determined *a*) by chemical correlation ((−)-**1a**), *b*) from the melting diagrams and mixed melting points (differential-scanning calorimetry *Fig. 1*) of the dinitrobenzoates of the CF_3-derivative (+)-**2a** and its CH_3-analogue **8**, and *c*) by X-ray analysis of the ester **2f** from (+)-**2a** and (−)-camphanoyl chloride (*Fig. 2* and *3*).

Enantiomerically pure 4,4,4-trichloro- and 4,4,4-trifluoro-3-hydroxybutanoic acid derivatives **1** and **2** are highly desirable chiral starting materials for organic synthesis. Thus, the β-lactone of (*S*)-4,4,4-trichloro-3-hydroxybutanoic acid was shown by *Wynberg & Staring* [1] to be accessible in 98% enantiomeric excess (ee) by quinidine-catalyzed asymmetric cycloaddition of ketene to chloral, and was hydrolyzed to (*S*)-malic acid, a source of numerous useful chiral building blocks [2]. In view of the interest in fluorinated analogues of biologically important natural products and drugs, an access to the chiral, non-racemic trifluoroester **2** would be even more important. Furthermore, it was interesting to find out, whether *Prelog*'s rule [3] for the enantioselective hydrogenation of carbonyl compounds by NADH-dependant enzymes of microorganisms (see **A**→**B**) would be followed by the trihalomethyl precursors of **1** and **2**, as it is for the 3-ketoesters which are reduced by baker's yeast *(Saccharomyces cerevisiae)* to the hydroxyester **3** [4–6], **4** [4], and **5** [7] of more than 90% ee[3]) (ee ≃ optical purity in the present paper).

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[1]) Part of the projected Ph. D. thesis of *P. R.*, ETH Zürich.

[2]) Part of the Dissertation No. 7514 of *M. Z.*, ETH Zürich, 1984.

[3]) For a comparison of such reductions by yeast and by a thermophilic microorganism, see [8].

1 2 A B

(+)-(*S*)-**3** (−)-(*R*)-**4** (*R*)-**5**

We now report on the preparative yeast reduction of ethyl 4,4,4-trichloro-3-oxobutanoate, readily available[4]) from trichloroacetyl chloride and ketene [9], and of ethyl 4,4,4-trifluoro-3-oxobutanoate, an inexpensive commercial product[5]). The (trifluoroaceto)acetate had been subjected to yeast reduction before by *Ishikawa & Kitazume* [10], but no determination of the absolute configuration was made, and a wrong value of the ee of the product **2** of reduction was reported[6])[7]).

Fermenting baker's yeast reduced ethyl (trichloroaceto)acetate[8]) (7 g/l, 30°, 20 h, 70%) to the hydroxyester (−)-(*S*)-**1a** of 84 to 88% ee. Enantiomerically pure product

(−)-(*S*)-**1a** R = C_2H_5
(−)-(*S*)-**1b** R = H

6

(+)-(*R*)-**2a** R = H
(+)-(*R*)-**2b** R = 3,5-$(NO_2)_2C_6H_3CO$
(*R*)-**2c** R = $CH(OC_2H_5)CH_3$ ≡ EE

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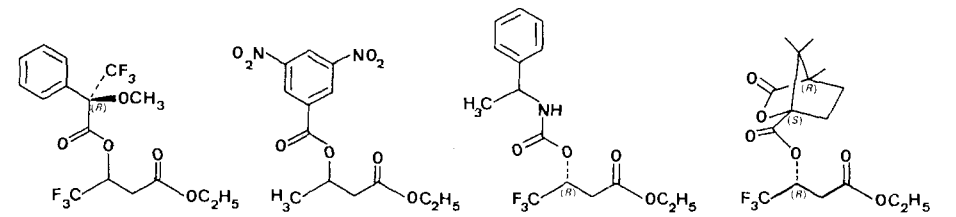

(3*R*,2′*R*)-**2d**
(3*S*,2′*R*)-**2d**

(−)-(*R*)-**8**
(+)-(*S*)-**8**
(±)-(*R*,*S*)-**8**

(3*R*,1′*R*)-**2e**
(3*R*,1′*S*)-**2e**

2f

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[4]) Ethyl 4,4,4-trichloro-3-oxobutanoate was prepared according to [9]. Instead of liquid SO_2, CH_2Cl_2 can be used as a solvent. We thank Drs. *A. Huwiler* and *L. Tenud* of the *Lonza AG*, Visp, for conveying this information to us, and we gratefully acknowledge their having provided us with a larger quantity of this ketoester.

[5]) We thank the *Lonza AG*, Visp, for generous gifts of ethyl 4,4,4-trifluoro-3-oxo-butanoate.

[6]) Simple trifluoro ketones have also been reduced previously by microbial or enzymatic methods [10] [11].

[7]) For a chemical correlation (COOH→CF_3) of the absolute configuration of a (trifluoromethyl)carbinol, see [12].

[8]) For early yeast reductions of mono-, di- and trichloromethyl ketones, see [13].

was readily obtained by removal of racemic (±)-**1a**, which crystallized preferentially from a methylcyclohexane solution at −10°. The optical purity was determined by saponification to the hydroxyacid (−)-**1b** which had a specific rotation $[\alpha]_{546} = -26.9°$ ([1]: +26.1°). The absolute configuration of (−)-**1a** was proved by conversion of (−)-(*S*)-**1b** to dextrorotatory dimethyl malate (**6**) of kown (*R*)-configuration [14], a process which has been proved to occur with inversion [1b].

Yeast reduction of ethyl (trifluoroaceto)acetate (15 g/l, 30°, 44 h) led to the isolation (75%) of the hydroxyester (+)-**2a**. The ee was determined by *Mosher*'s method [15] from the ^{1}H-NMR spectrum of the diastereoisomeric diesters **2d**, a 1:1 mixture of which was prepared from racemic trifluoro-hydroxy-butanoate (±)-**2a**. An ee-value of 49–51% resulted[9]). This was confirmed by preparing (+)-**2a** of a very high ee using two procedures: *a*) upon cooling a solution of (+)-**2a** of *ca.* 45% ee in pentane/Et_2O to −20°, (±)-**2a** crystallized, and the mother liquor contained (+)-**2a** of 92% ee; *b*) upon crystallization of the 3,5-dinitrobenzoate (+)-**2b** of *ca.* 45% ee, the (±)-form remained in solution, so that two crystallizations from Et_2O/pentane furnished (+)-**2b** from which trifluoro-hydroxyester (+)-**2a** of more than 98% ee[10]) was obtained by titanate-catalyzed transesterification [16–18][11]). Thus, the trifluoro-hydroxyester (+)-**2a** is now available in > 98% ee on a preparative scale, as starting material for EPC (enantiomerically pure compounds) syntheses [2] (see the ethoxyethyl(EE)-protected diol **7**, obtained in 78% yield from (*R*)-**2c** by $LiAlH_4$ reduction). Attempts to improve the enantioselectivity of the yeast reduction, for instance by using aerobic conditions [6], have so far been unsuccessful. But we are confident to find soon another microorganism which will lead to higher optical yields than baker's yeast (*cf.* [21] [8]). Since it was conceivable that the highly reactive trifluoromethyl ketone is reduced to **2a** by the free coenzyme NADH, and not by an enzyme-coenzyme complex, we also tested this possibility and found that equimolar amounts of NADH, in the absence of yeast and enzyme, cause no reduction at 30° in H_2O.

As will be shown in the following section, the absolute configuration of (+)-**2a** is (*R*). Thus, the hydride transfer to the keto group has taken place from the *Si*-face; this is the opposite steric course as compared with the trichloro-ester (→(−)-**1a**) which is reduced from the *Re*-face. Since it may be assumed that the CCl_3-group is sterically more demanding than the CH_3- and CF_3-groups, the conclusion is that *Prelog*'s rule (see **A**→**B**) holds for the yeast reduction of the highly halogenated carbonyl compounds, trifluoro- and trichloro-3-oxobutanoate: CF_3 is $R_{(small)}$ in **A**, just like CH_3, while CCl_3 is $R_{(large)}$ in **A**.

The sense of chirality of the trifluorohydroxyester **2a** was determined by two independant methods, a correlative one, and an absolute one. For correlation with the ethyl 3-hydroxybutanoates of known absolute configuration, we prepared the (−)-(*R*) [17], the (+)-(*S*) [5] [6] [20], and the (±)-dinitrobenzoates **8**, and measured the melting curves of mixtures of enantiomers and of mixtures of the CH_3- and CF_3-derivatives **8** and **2b** calorimetrically (differential-scanning calorimetry). The resulting melting-point

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[9]) With another NMR method, a 94% ee was previously assigned [10] to a sample of *ca.* 50% ee.

[10]) The calorimetrically determined melting curve of (+)-**2b** indicates a purity of 99.2%.

[11]) The resolution [19] of (±)-3,5-dinitrobenzoates and the enrichment [20] [21] of partially resolved 3,5-dinitrobenzoates was shown by us to be possible in many other cases as well.

diagrams were compared with those calculated by the *Schröder-Van-Laar-Le Chatelier* equation (for simple eutectic) and by the *Prigogine-Defay* equation (for true racemic mixtures) [22] (for details see the *Exper. Part*). For general discussions, see the articles by *Raznikiewicz* [23] and *Ricci* [24], and for cases analogous to the present one, see the applications published by *Cram et al.* and *Mislow et al.* [25]. *Fig. 1* shows the measured melting points of and the calculated curves for: *A:* mixtures of (+)- and (−)-CF_3-benzoates **2b**; *B*: mixtures of (+)-(*S*)- and (−)-(*R*)-CH_3-benzoates **8**; *C*: mixtures of (+)-

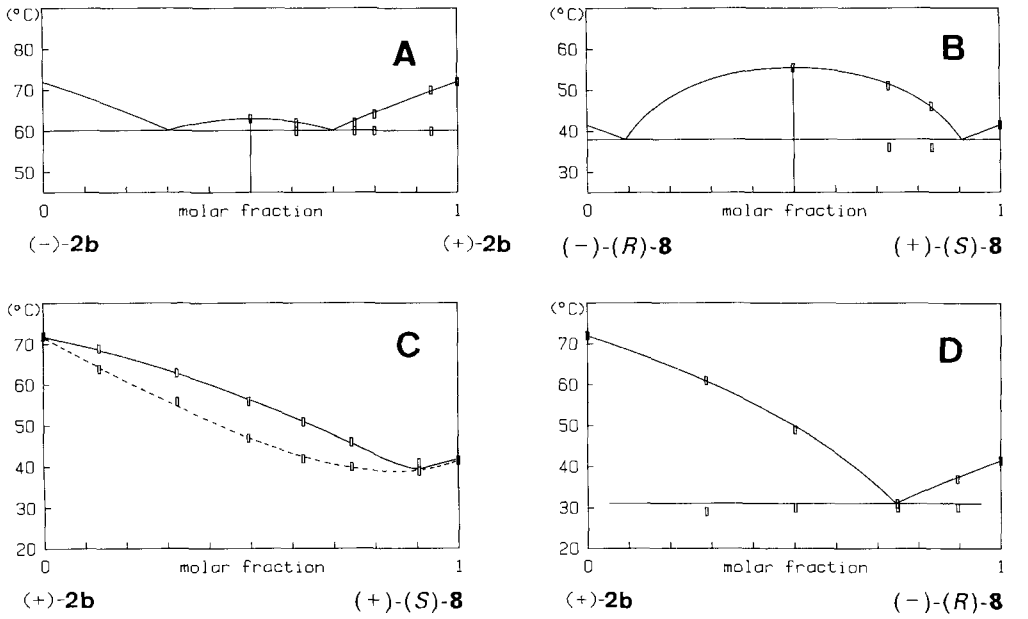
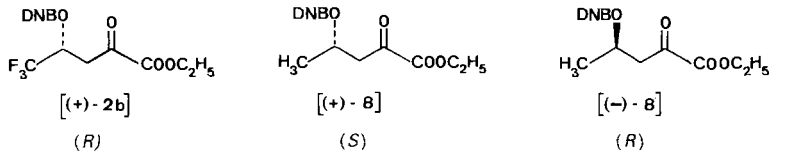


Fig. 1. *Melting phase diagrams of mixtures of the 3,5-dinitrobenzoates* **2b** *and* **8**. *A* and *B* are the diagrams of enantiomeric mixtures of **2b** and **8**, respectively. *C* and *D* are phase diagrams obtained with mixtures of (+)-**2b** of 99.2% purity with (+)-**8** and (−)-**8**, respectively. The *solidus* (lower, beginning of melting) and *liquidus* (upper, end of melting) curves were also calculated in the cases *A*, *B*, and *C*. (+)-**2b** and (+)-**8** form solid solutions (*C*), (+)-**2b** and (−)-**8** do not mix in the solid state (eutectic mixture *D*).

CF_3-benzoate **2b** and (+)-(*S*)-CH_3-benzoate **8**, and *D*: mixtures of (+)-CF_3-benzoate **2b** and (−)-(*R*)-CH_3-benzoate **8**. It is evident from *Fig. 1* that both enantiomeric mixtures (**2b** and **8**) exhibit the normal melting behaviour of compounds forming a racemate, see the *solidus/liquidus* curves in the phase diagrams *A* and *B*. No pair of CF_3- and CH_3-benzoates forms a quasiracemate according to *Fredga* [26]. However, (+)-**2b** and (+)-(*S*)-**8** form mixed crystals, see diagram *C*, while (+)-**2b** and (−)-(*R*)-**8** give rise to an eutectic mixture, *i.e.* are non-miscible in the solid state, see diagram *D*. This suggests that the two dextrorotatory stereoisomers [(+)-**2b** and (+)-**8**] are isomorphous, while the pair of opposite sense of rotation [(+)-**2b** and (−)-**8**] has opposite chirality [22]. Thus, with the reversal of the CIP-priority [27] sequence brought about by the fluoro substitution, the specification of the sense of chirality of the product of yeast reduction, (+)-**2a**, would be (*R*):



DNBO = 3,5–$(NO_2)_2C_6H_3CO$

For definitive proof, we sought for a crystalline, diastereoisomerically pure ester of (+)-**2a** with an acid of known absolute configuration. From an X-ray crystal structure determination of such an ester, the relative configuration, and hence the absolute configuration at the (trifluoromethyl)carbinol center would be assigned. We prepared both diastereoisomers of **2e** from (*R*)- and (*S*)-(1-phenylethyl) isocyanate and (+)-**2a**, but the beautiful needles of neither diastereoisomer were single crystals. However, the ester **2f** obtained from (−)-camphanoyl chloride[12]) and (+)-**2a** furnished single crystals suitable for X-ray analysis, from which the relative and absolute configuration follows as specified in the *Formula* **2f**.

The molecule **2f** is shown in *Fig. 2* and its crystal-packing in *Fig. 3*. The asymmetric unit contains two molecules that are related by a non-crystallographic two-fold screw axis at $x = 0.5$ and $z = 0.25$ with a translation of 0.4 fractional units in the *b*-direction. This is equivalent to a non-crystallographic translation to another asymmetric unit. Because of the disorder of the ethyl-ester groups and the general high thermal motion of the molecule little significance can be attributed to the individual bond-lengths and the differences between the two molecules.

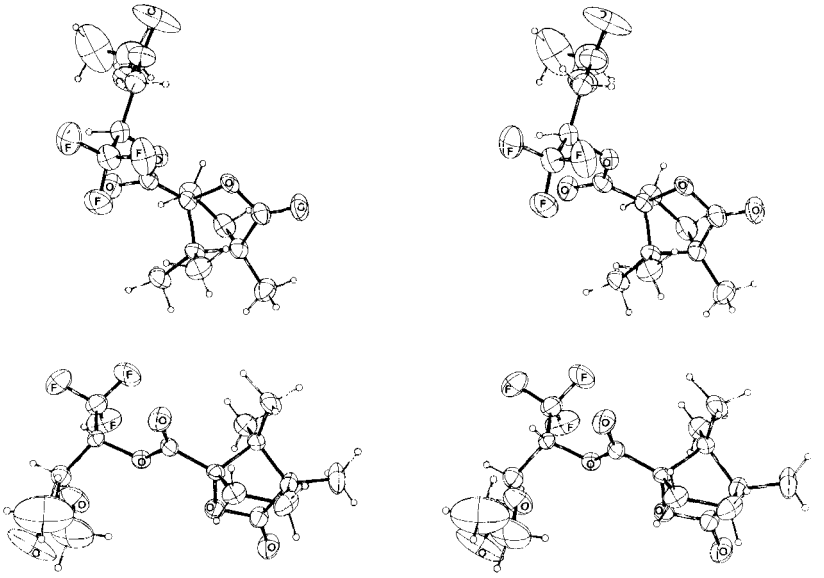


Fig. 2. *ORTEP* [29] *stereoview of the two molecules of* **2f**. Vibrational ellipsoids are drawn at the 25% probability level.

[12]) Obtained from (+)-(*R*,*R*)-camphor [28].

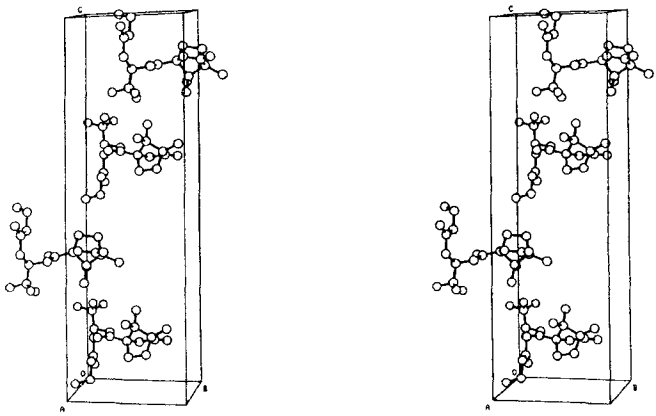


Fig. 3. *Stereoview of the unit cell of* **2f**

The isomorphism of the two dinitrobenzoates (+)-**2b** and (+)-**8** is thus confirmed by the X-ray analysis of the camphanic acid derivative **2f**. The fact that (+)-**2b**-(*R*) and (+)-**8**-(*S*) form mixed crystals is yet another proof that CH_3 and CF_3 can replace each other, *i.e.* that the size of these two groups is very similar. On the other hand, the fact that (+)-(*R*)-**2b** and (−)-(*R*)-**8** do not form a quasiracemate might be interpreted as a consequence of the different polarity, acidity and H-bond-forming ability of the $CH_3CH(OH)$ and $CF_3CH(OH)$ moieties. To test the differences of interactions of these two moieties with enzyme active sites, we plan to synthesize from **2a** some CF_3-analogues of biologically active compounds.

Experimental Part

A) General Remarks. – Fresh baker's yeast (*Klipfel & Co. AG*, Rheinfelden) and commercially available saccharose were used for the reactions. For flash column chromatography, *Merck* silica gel *60* (230–400 mesh) was used. Melting points (m.p.) were determined by using a *Büchi 510* apparatus. Bulb-to-bulb distillations were carried out by using a *Büchi GKR-50* and *Chemophor Custilator* depending on the scale; boiling points (b.p.) refer to air-bath temperatures. All b.p. and m.p. are uncorrected. The following instruments were used: Capillary GC: *Carlo Erba HRGC Fractovap* series *4160*. Specific rotation: *Perkin-Elmer-241* polarimeter. IR: *Perkin-Elmer 297* spectrometer (film, $CHCl_3$), *Perkin-Elmer-283* spectrometer (KBr). ^{1}H-NMR: *Varian EM-390* (90 MHz) and *Bruker WM 300-WB* (300 MHz); unless otherwise indicated, the reported spectra were recorded at 90 MHz, chemical shifts given in ppm, with TMS signal at 0 ppm.

B) Preparations. – *Ethyl (S)-4,4,4-Trichloro-3-hydroxybutanoate* ((−)-**1a**). In a 6-l flask, baker's yeast (500 g) was dispersed at 30° in a solution of saccharose (560 g) in tap water (3 l). After 0.5 h, ethyl 4,4,4-trichloro-3-oxobutanoate (20 g, 86 mmol) was added. The solution was allowed to stir for 20 h at 30° until no more starting material was left (capillary GC, *SE-54*, 13.5 m, 130°). The mixture was filtered through a sintered glass funnel (porosity 4), the filtrate was extracted 4× with 1 l of AcOEt, and the combined extracts were dried ($MgSO_4$). The solvent was evaporated. Short-path distillation *in vacuo* gave (−)-**1a** (14.2 g, 70%), b.p. 82–92°/0.01 Torr, $[\alpha]_D^{20} = -20.1°$ (*c* = 1.1, $CHCl_3$). For enrichment, the 14.2 g of (−)-**1a** (84% ee) were dissolved in 28 ml of methylcyclohexane and cooled to −10°. The precipitate (racemate) was filtered off and the solvent evaporated. Bulb-to-bulb distillation of the residue gave (−)-**1a** (10.5 g, 52%), b.p. 130°/0.01 Torr, $[\alpha]_D^{20} = -24.0°$ (*c* = 1.1, $CHCl_3$). IR ($CHCl_3$): 3575*m*, 3410*w* (br.), 2980*m*, 2935*w*, 2900*w*, 1719*s*, 1390*m*, 1370*s*, 1348*m*, 1095*s*, 1025*m*, 1000*w*, 900*w*. ^{1}H-NMR ($CDCl_3$): 1.30 (*t*, *J* = 7, 3H, CH_2CH_3O); 2.60–2.87 (*A* of *ABX*, J_{AB} = 17, J_{AX} = 9, 1H, H–C(2)); 2.97–3.20 (*B* of *ABX*, J_{BA} = 17, J_{BX} = 3, 1H, H–C(2)); 3.70 (br. *s*, 1H, OH), 4.20 (*q*, *J* = 7, 2H,

CH_2CH_3O); 4.63 (*dd*, *X* of *ABX*, $J_{XA} = 9$, $J_{XB} = 3$, 1H, H–C (3)). Anal. calc. for $C_6H_9Cl_3O_3$ (235.50): C 30.60, H 3.85; found: C 30.78, H 4.01.

(S)-4,4,4-Trichloro-3-hydroxybutanoic Acid ((–)-**1b**). A solution of (–)-**1a** (2.9 g, 12.3 mmol) in 4N HCl (46.5 ml) was heated at reflux during 2.5 h. The solution was allowed to cool to r.t. and was evaporated under high vacuum (30–35°). The crystals were dried overnight under high vacuum and then 15 min at 100°. Colorless crystals of (–)-**1b** (2.36 g, 92%) were obtained, $[\alpha]_D^{20} = -23.0°$ ($c = 1.2$, acetone), $[\alpha]_{546}^{20} = -26.9°$ ($c = 1.2$, acetone) ([1]: $[\alpha]_{546}^{20} = +26.1°$ ($c = 1$, acetone)). ^{1}H-NMR (D_2O): 2.53–2.87 (*A* of *ABX*, $J_{AB} = 17$, $J_{AX} = 10$, 1H, H–C(2)); 3.10–3.37 (*B* of *ABX*, $J_{BA} = 17$, $J_{BX} = 2$, 1H, H–C(2)); 4.53–4.80 (*m*, 3H, H–C(3), HDO).

Dimethyl (R)-Malate (**6**). NaOH (2.2 g, 55 mmol) in 15 ml H_2O was added dropwise at 0° to a solution of (–)-**1b** (2.08 g, 10 mmol) in H_2O (15 ml). The mixture was stirred at r.t. for 24 h and finally acidified by passing through a column of the ion-exchange resin *Lewatit S 100* (150 g). The solution was evaporated under high vacuum and dried overnight under high vacuum. To the residue were added 11 ml of abs. MeOH and 63 mg (0.33 mmol) of $TsOH \cdot H_2O$, the mixture was heated 8 h at reflux. Then, 7 ml of CCl_4 were added and the solvent was evaporated. After again adding 11 ml of MeOH, the mixture was heated 12 h at reflux, whereupon 7 ml of CCl_4 were added. The solution was concentrated to 2 ml which were dissolved in 10 ml of Et_2O, washed with 2 ml of sat. $NaHCO_3$-solution and 2 ml of sat. NaCl-solution, and dried ($MgSO_4$). After removal of the solvent, bulb-to-bulb distillation gave **6** (1.07 g, 66%) as a colorless oil; b.p. 85–100°/0.05 Torr, $[\alpha]_D^{20} = +7.16°$ (neat) ([30]: $[\alpha]_D = -6.9$ (neat)). ^{1}H-NMR ($CDCl_3$): 2.77–2.87 (*m*, 2H, 2H–C(3)); 3.33 (*d*, $J = 6$, 1H, OH); 3.70 (*s*, 3H, CH_3O); 3.80 (*s*, 3H, CH_3O); 4.40–4.60 (*m*, 1H, H–C(2)).

Optically Active Ethyl 4,4,4-Trifluoro-3-hydroxybutanoate ((+)-**2a**) *by Yeast Reduction of the Ketoester*. In a 6-l flask, baker's yeast (336 g) was dispersed at 30° in a solution of saccharose (600 g) in tap water (3.2 l). After 0.5 h, ethyl 4,4,4-trifluoro-3-oxobutanoate (48 g, 261 mmol) was added. The solution was allowed to stir for 30 h at 30°. The mixture was centrifuged and the liquid phase extracted 4× with 1 l Et_2O. The combined extracts were dried ($MgSO_4$). Et_2O was evaporated and distillation gave (+)-**2a** (36.4 g, 75%), b.p. 75°/11 Torr, $[\alpha]_D^{20} = +10.1°$ ($c = 0.9$, $CHCl_3$). IR ($CHCl_3$): 3580*m*, 3420*m* (br.), 2975*m*, 2935*w*, 2900*w*, 1715*s*, 1369*m*, 1018*m*, 948*w*, 898*w*, 875*s*. ^{1}H-NMR ($CDCl_3$): 1.28 (*t*, $J = 7.5$, 3H, CH_2CH_3O); 2.63–2.75 (*m*, 2H, H–C(2)); 3.67 (*s*, 1H, OH); 4.20 (*q*, $J = 7.5$, 2H, CH_2CH_3O); 4.27–4.57 (*m*, 1H, H–C(3)). Anal. calc. for $C_6H_9O_3F_3$ (186.13): C 38.72, H 4.87; found: C 38.68, H 4.97.

For enrichment, 36.4 g of (+)-**2a** were dissolved in 65 ml of pentane/Et_2O 20:1 and cooled to –20°. The racemate crystallized and was removed by filtration, and the remaining solvent was evaporated. Bulb-to-bulb distillation of the residue gave (+)-**2a** (14.0 g, 28% from the ketoester); b.p. 90–100°/11 Torr, $[\alpha]_D^{20} = +20.1°$ ($c = 1.0$, $CHCl_3$).

A racemic sample, (+)-**2a** was prepared for comparison by $NaBH_4$-reduction of the ethyl ester in i-PrOH. On a 10 g-scale, the yield was 60%. After bulb-to-bulb distillation, (±)-**2a** had a m.p. of 16°.

For determination of the optical purity of (+)-**2a** from the yeast reduction, samples of both (±)-**2a** and (+)-**2a** ($[\alpha]_D^{20} = +10.1°$ ($c = 0.9$, $CHCl_3$)), were converted to *ethyl 4,4,4-trifluoro-3-[(R)-3',3',3'-trifluoro-2'-methoxy-2'-phenylpropionyloxy]butanoate* (**2d**), following *Mosher*'s procedure [15]. From the ^{1}H-NMR spectra of these derivatives an ee of 49–51% was determined (ratio of diastereoisomers *ca.* 75:25). Major diastereoisomer (3*R*, 2'*R*)-**2d**: ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20 (*t*, $J = 7$, 3H, OCH_2CH_3); 2.76–2.80 (*m*, 2H, H–C(2)); 3.56 (*q*, $J = 1$, 3H, CH_3O); 4.09 (*q*, $J = 7$, CH_2CH_3O); 5.98–6.05 (*m*, 1H, H–C(3)); 7.36–7.53 (*m*, 5H, arom. H). Minor diastereoisomer (3*S*, 2'*R*)-**2d**: ^{1}H-NMR (300 MHz, $CDCl_3$): 1.25 (*t*, $J = 7$, 3H, CH_2CH_3O); 2.85–2.87 (*m*, 2H, H–C(2)); 3.51 (*q*, $J = 1$, CH_3O); 4.17 (*m*, 2H, CH_2CH_3O); 5.98–6.05 (*m*, 1H, H–C(3)); 7.36–7.53 (*m*, 5H, arom. H).

Ethyl (R)-3-(3',5'-Dinitrobenzoyloxy)-4,4,4-trifluorobutanoate ((+)-**2b**). A solution of dinitrobenzoyl chlorid (46.2 g, 200 mmol) in 130 ml of dry Et_2O/CH_2Cl_2 1:1 was added dropwise to a second solution of (+)-**2a** (36.4 g, 196 mmol, from yeast reduction) in Et_2O (180 ml) and Et_3N (28 ml, 203 mmol). The addition was conducted at 4° under Ar within 30 min. The red-brown solution was allowed to stir for 2.5 h at r.t. $Et_3N \cdot HCl$ was filtered off, the filtrate was extracted with a sat. $NaHCO_3$-solution, washed with a sat. NaCl-solution and dried ($MgSO_4$). Removal of the solvent gave yellowish crystals of crude (+)-**2b** (67.5 g, 91%); m.p. 58.5–63°, $[\alpha]_D^{20} = +11.1°$ ($c = 1.0$, $CHCl_3$).

For enantiomeric enrichment, this material was dissolved in hot Et_2O (350 ml) and filtered, if necessary. To the clear solution was added pentane (210 ml). After 0.5 h of vigorous stirring at r.t., the crystals of (+)-**2b** were filtered off. A small portion was dried under high vacuum; m.p. 70.5–72°, $[\alpha]_D^{20} = +20.0°$ ($c = 1.1$, $CHCl_3$). After repeating the recrystallization with 130 ml Et_2O/80 ml pentane and drying under high vacuum, colorless crystals of (+)-**2b** (20.1 g, 27% from (+)-**2a**) were obtained; m.p. 71.8–72.2°, $[\alpha]_D^{20} = +21.9°$ ($c = 1.1$, $CHCl_3$). IR (KBr): 3440*w* (br.), 3120*w*, 3097*w*, 3000*w*, 2985*w*, 1749*s*, 1729*s*, 1630*m*, 1600*w*, 1554*s*, 1461*w*, 1426*w*, 1372*m*, 1346*s*,

1328*w*, 1312*m*, 1281*s*, 1267*s*, 1223*w*, 1191*s*, 1163*m*, 1134*s*, 1103*w*, 1077*w*, 1040*m*, 1011*w*, 945*w*, 930*w*, 918*m*, 886*m*. ^{1}H-NMR ($CDCl_3$): 1.23 (*t*, *J* = 7, 3H, CH_2CH_3O); 2.95–3.05 (*m*, 2H, H–C(2)); 4.15 (*q*, *J* = 7, 2H, CH_2CH_3O); 5.90–6.32 (*m*, 1H, H–C(3)); 9.13–9.33 (*m*, 3H, arom. H). Anal. calc. for $C_{13}H_{11}F_3N_2O_8$ (380.24): C 41.07, H 2.92, N 7.37; found: C 40.98, H 3.04, N 7.26.

For comparison, a sample of the racemic dinitrobenzoate (±)-**2b** (m.p. 63–64°, from Et_2O/pentane) was prepared from (±)-**2a**.

*Ethyl (*R*)-4,4,4-Trifluoro-3-hydroxybutanoate ((+)-***2a***) from Enantiomerically Enriched Dinitrobenzoate* (+)-**2b**. EtOH (330 ml) of (+)-**2b** (20.1 g, 53 mmol; $[\alpha]_D^{20}$ = +21.9° (*c* = 1.1, $CHCl_3$)), and tetraethyltitanate (3.0 g, 13 mmol) were heated for 31 h at reflux. After cooling to r.t., the solution was filtered from ethyl 3,5-dinitrobenzoate, concentrated to 50 ml, and filtered again. The filtrate was mixed with 50 ml of a sat. NaF-solution, filtered, and the filter cake washed with 20 ml of pentane/H_2O 1:1. The resulting heterogeneous mixture was extracted 4× with CH_2Cl_2. The combined org. extracts were dried ($MgSO_4$) and condensed. Bulb-to-bulb distillation gave (+)-**2a** (8.0 g, 81%); b.p. 100–110°/11 Torr, d_4^{25} = 1.237 g/cm^3, $[\alpha]_D^{20}$ = +21.8 (*c* = 1.25, $CHCl_3$), $[\alpha]_D^{20}$ = +20.7° (neat).

If the sample thus obtained is assumed to be optically pure, the product of yeast reduction has an ee of 46%, in reasonable agreement with the value determined by *Mosher's* method. By the same token, the sample from direct enrichment by low-temperature crystallization of **2a** has an ee of 92%.

*Ethyl (*R*)-4,4,4-Trifluoro-3-[*N*-((*S*)-1'-phenylethyl)carbamoyloxy]butanoate* ((3*R*, 1'*S*)-**2e**). To a toluene solution (1 ml) of (+)-**2a** (589 mg, 3.17 mmol) and of (*S*)-1-phenylethyl isocyanate (*Fluka, purum;* 465 mg, 3.16 mmol) was added 4-(*N,N*-dimethyl-amino)pyridine (*Fluka, purum;* 6 mg, 0.05 mmol). The mixture was allowed to stir for 2 h at 100° ($CaCl_2$ drying tube), then 5 ml of MeOH were added, and the solution was heated again for 5 min. After evaporation, crude (3*R*, 1'*S*)-**2e** was recrystallized from MeOH/H_2O and then from Et_2O/pentane to give colorless needles; m.p. 93.5–94°, $[\alpha]_D^{20}$ = –30.2° (*c* = 0.9, $CHCl_3$). IR (KBr): 3440*w* (br.), 3330*m*, 3070*w*, 2995*m*, 2980*w*, 2935*w*, 1740*s*, 1715*s*, 1685*w*, 1590*w*, 1545*s*, 1500*w*, 1450*m*, 1390*m*, 1370*m*, 1360*m*, 1350*m*, 1300*m*, 1290*m*, 1260*s*, 1245*s*, 1190*s*, 1185*s*, 1160*m*, 1135*s*, 1115*m*, 1065*m*, 1035*m*, 1030*m*, 880*w*, 860*w*, 760*m*, 700*m*, 680*w*, 660*m*. ^{1}H-NMR ($CDCl_3$): 1.25 (*t*, *J* = 7, 3H, CH_2CH_3O); 1.50 (*d*, *J* = 7, 3H, H–C(2')); 2.60–2.83 (*m*, 2H, H–C(2)); 4.18 (*q*, *J* = 7, 2H, CH_2CH_3O); 4.63–5.26 (*m*, 2H, NH and H–C(1')); 5.66 (*sext.*, *J* = 7, 1H, H–C(3)); 7.20–7.41 (*m*, 5H, arom. H). Anal. calc. for $C_{15}H_{18}F_3NO_4$ (333.31): C 54.05, H 5.44, N 4.20; found: C 54.24, H 5.29, N 4.47.

*Ethyl (*R*)-4,4,4-Trifluoro-3-[*N*-((*R*)-1'-phenylethyl)carbamoyloxy]butanoate* ((3*R*, 1'*R*)-**2e**). Using the procedure for (3*R*, 1'*S*)-**2e** (see above), (+)-**2a** (500 mg, 2.69 mmol) and (*R*)-1-phenylethyl isocyanate (*Fluka, purum;* 395 mg, 2.69 mmol) were combined to give (3*R*, 1'*R*)-**2e**; m.p. 81.5–82.0°, $[\alpha]_D$ = +57.3° (*c* = 0.8, $CHCl_3$). IR (KBr): 3440*w* (br.), 3360*m*, 3070*w*, 3040*w*, 2990*m*, 2940*w*, 1740*s*, 1715*s*, 1530*s*, 1500*m*, 1450*m*, 1395*m*, 1380*m*, 1370*m*, 1330*m*, 1315*m*, 1305*m*, 1290*m*, 1260*s*, 1245*s*, 1190*s*, 1150*m*, 1130*s*, 1120*m*, 1095*m*, 1065*m*, 1030*m*, 1010*w*, 1000*w*, 920*w*, 880*w*, 860*w*, 760*m*, 700*m*, 660*m*, 640*w*, 610*w*, 550*w*, 520*w*. ^{1}H-NMR ($CDCl_3$): 1.10 (*t*, *J* = 7, 3H, CH_2CH_3O); 1.40–1.60 (*m*, 3H, H–C(2')); 2.60–2.73 (*m*, 2H, H–C(2)); 4.00 (*q*, *J* = 7, 2H, CH_2CH_3O); 4.63–5.23 (*m*, 2H, NH, H–C(1')); 5.60 (*sext.*, *J* = 7, 1H. H–C(3)); 7.06–7.36 (*m*, 5H, arom. H). Anal. calc. for $C_{15}H_{18}F_3NO_4$ (333.31): C 54.05, H 5.44, N 4.20; found: C 54.04, H 5.36, N 4.22.

*Ethyl (3*R*)-4,4,4-Trifluoro-3-[(1'*S*,4'*R*)-3'-oxo-4',7',7'-trimethyl-2'-oxabicyclo[2.1.1]heptane-1'-carbonyloxy]butanoate* (**2f**). A solution of (+)-**2a** (0.93 g, 5 mmol) and of (–)-camphanoyl chloride (*Fluka, purum;* 1.63 g, 7.5 mmol) in pyridine (*Fluka, puriss.;* dist. over KOH; 20 ml) was allowed to stir for 20 h at r.t. After addition of CH_2Cl_2 (50 ml), the org. phase was washed with 2N HCl followed by sat. NaCl-solution. The resulting solution was dried ($MgSO_4$) and evaporated. Flash chromatography (100 g SiO_2, CH_2Cl_2/Et_2O, 20:1) of the residue gave **2f** (1.80 g, 97%). Recrystallization from pentane/CH_2Cl_2 20:1 gave crystals suitable for X-ray analyses; m.p. 68.6–69.2°, $[\alpha]_D^{20}$ = +0.81° (*c* = 1.6, $CHCl_3$). IR (KBr): 3450*w* (br.), 2980*m*, 2950*w*, 1785*s*, 1755*s*, 1740*s*, 1470*w*, 1450*w*, 1400*m*, 1380*m*, 1360*m*, 1340*m*, 1320*m*, 1290*m*, 1260*s*, 1180*s*, 1170*s*, 1140*s*, 1105*s*, 1090*s*, 1055*s*, 1035*m*, 1010*m*, 990*m*, 960*w*, 930*m*, 900*w*, 650*w*. ^{1}H-NMR ($CDCl_3$): 0.97, 1.05, 1.12 (3*s*, 9H, CH_3–C(4'), 2 CH_3–C(7')); 1.25 (*t*, *J* = 7, 3H, CH_3CH_2O); 1.43–2.67 (*m*, 4H, 2H–C(5'), 2H–C(6')); 2.85 (*d*, *J* = 6, 2H, 2H–C(2)); 4.18 (*q*, *J* = 7, 2H, CH_3CH_2O); 5.92 (*sext.*, *J* = 6, 1H, H–C(3)). Anal. calc. for $C_{16}H_{21}F_3O_6$ (366.34): C 52.46, H 5.78; found: C 52.22, H 5.62.

Ethyl 3-(1'-Ethoxyethoxy)-4,4,4-trifluorobutanoate ((*R*)-**2c**). A solution of (+)-**2a** (1.86 g, 10 mmol) in ethyl vinyl ether (17 ml) was stirred for 18 h at r.t. with CF_3COOH (0.1 ml). The mixture was washed with a sat. $NaHCO_3$-solution and dried (Na_2SO_4). Evaporation of the solvent gave (*R*)-**2c** (2.55 g, 99%), used without further purification for the preparation of **7**. ^{1}H-NMR: 1.07–1.38 (*m*, 9H, 3 CH_3); 2.60–2.73 (*d*, 2H, 2H–C(2)); 3.31–3.80 (*m*, 2H, $CHOCH_2CH_3$); 4.17 (*q*, *J* = 7, $COOCH_2CH_3$); 4.47 (*quint.*, *J* = 7.5, H–C(3)); 4.80–4.97 (*m*, 1H, $OCH(CH_3)O$).

3-(1'-Ethoxyethoxy)-4,4,4-trifluoro-1-butanol (**7**). An ethereal solution (2.4 ml) of **2c** (2.55 g, 9.9 mmol) was added dropwise over 30 min at −10 to 0° to a suspension of $LiAlH_4$ (0.25 g, 6.5 mmol) in Et_2O (7.5 ml). After stirring for 2.5 h at r.t., H_2O (0.24 ml), KOH (0.24 ml, 15%) and H_2O (0.72 ml) were added successively, and the solution was stirred for an additional 5 min. The precipitate was filtered off and washed 2× with hot CH_2Cl_2. The combined extracts were dried (Na_2SO_4), condensed, and purified by bulb-to-bulb distillation to give **7** (1.67 g, 78%); b.p. 50–65°/0.01 Torr. IR (film): 3440*m* (br.), 1278*m*, 1166*s*, 1130*s*, 1090*m* (br.), 950*w*, 910*w*. ^{1}H-NMR: 1.08–1.45 (*m*, 6H, 2 CH_3); 1.68–2.10 (*m*, 2H, 2H–C(2)); 2.92 (*t*, *J* = 7, 1H, OH); 3.41–3.93 (*m*, 4H, H–C(1), COOCH_2CH$_3$); 4.00–4.33 (*m*, 1H, H–C(3)); 4.73–5.00 (*m*, 1H, OC*H*(CH$_3$)O).

Ethyl (S)-3-(3',5'-dinitrobenzoyloxy)butanoate ((+)-**8**). According to the procedure used for the preparation of (+)-**2b**, (+)-(*S*)-**3** [20] (6.61 g, 50 mmol) was processed. Recrystallization from Et_2O/pentane 10:3 gave pale-yellow crystals of (+)-**8** (11.2 g, 68%). Two further recrystallizations gave pure (+)-**8**-(*S*); m.p. 40.4–40.8°, $[\alpha]_D^{20}$ = +26.2 (*c* = 1.0, $CHCl_3$) ([20]: m.p. 40–41°, $[\alpha]_D^{25}$ = +26.0° (*c* = 1.4, $CHCl_3$)). See [20] for spectral data.

Ethyl (R)-3-(3',5'-Dinitrobenzoyloxy)butanoate ((−)-**8**). This sample was prepared from (−)-(*R*)-**3** [17] exactly as described for the (+)-enantiomer; m.p. 41.0–41.6°, $[\alpha]_D^{20}$ = −25.8° (*c* = 1.0, $CHCl_3$).

Ethyl (±)-3-(3',5'-Dinitrobenzoyloxy)butanoate (**8**). Racemic **3** *(Fluka, purum)* was converted to (±)-**8** as described for the optically pure samples; m.p. 55.4–56.2°.

C) Differential-Scanning Calorimetry of the Dinitrobenzoates 2b and 8. – A microcalorimeter *Perkin-Elmer DSC 2* was used for measuring the melting curves (mcal/sec *vs. Kelvin*). The following abbreviations will be used: T_i (beginning of melting), T_f (end of melting). The pure dinitrobenzoates gave rise to narrow melting curves indicating high purity. The melting points and enthalpies of fusion thus determined are given in *Table 1*. The values allow the calculation of the diagrams (see *Fig. 1 A, 1B, and 1D* and *Tables 2, 3,* and *5*).

Table 1. *Melting Data of Pure Dinitrobenzoates*

Dinitrobenzoate	M.p.		Enthalpies of fusion
	[°]	[K]	[kcal/mol]
(+)-**2b**	72.0	345.2	6.95
(±)-**2b**	63.0	336.2	6.75
(−)-(*R*)-**8**	41.5	314.7	5.4
(+)-(*S*)-**8**	41.0	314.2	5.5
(±)-**8**	55.5	328.7	6.3

Table 2. *Melting Behaviour of Mixtures of (+)- and (−)-***2b** (see *Fig. 1A*)

Enantiomeric excess [%]	T_i (calc.) [°]	T_i (exp.)[a] [°]	T_f (calc.) [°]	T_f (exp.)[a] [°]
22.07	60.2	60 ± 1	62.2	62 ± 1
59.70	60.2	60 ± 1	64.5	64 ± 1
50.13	60.2	60 ± 1	62.5	62 ± 1
87.15	60.2	60 ± 1	69.8	70 ± 1

[a]) The measured temperatures [*T*(exp.)] were obtained after heating the solid mixtures for several at 45°, otherwise complex curves due to crystalline polymorphism were obtained. No polymorphism was observed with the pure compounds.

Table 3. *Melting Behaviour of Mixtures of (+)-(S)- and (−)-(R)-***8** (see Fig. *1B*)

Enantiomeric excess [%]	T_i (calc.) [°]	T_i (exp.) [°]	T_f (calc.) [°]	T_f (exp.) [°]
66.77	38.0	36 ± 1	45.7	46 ± 1
46.10	38.0	36 ± 1	51.5	51 ± 1

The melting behaviour of mixtures of the enantiomerically pure dinitrobenzoates from CH_3- and CF_3-hydroxybutanoates are given in *Table 4* and *5*.

Table 4. *Melting Behaviour of mixtures of (+)-***2b** *and (+)-(S)-***8**[a]) (see *Fig. 1C*)

Molar composition [%]		Temperatures [°]	
(+)-(*S*)-**8**	(+)-**2b**	T_i (exp.)[a])	T_f (exp.)
90.47	9.53	39 ± 1	41 ± 1
74.30	25.70	40 ± 1	46 ± 1
62.63	37.73	42 ± 1	51 ± 1
49.53	50.47	47 ± 1	56 ± 1
42.26	67.74	56 ± 1	64 ± 1
13.51	86.49	64 ± 1	69 ± 1

[a]) In this case, the beginning of melting is difficult to determine. We have arbitrarily chosen the point at which 5–10% of the material was molten.

Table 5. *Melting Behaviour of Mixture of (+)-***2b** *and (−)-(R)-***8** (see *Fig. 1D*)

Molar compositon [%]		T_i (calc.)	T_i (exp.)	T_f (calc.)	T_f (exp.)
(−)-(*R*)-**8**	(+)-**2b**	[°]	[°]	[°]	[°]
89.45	10.55	31.1	30 ± 1	37.5	37 ± 1
74.79	25.21	31.1	30 ± 1	31.3	31 ± 1
50.07	49.93	31.1	30 ± 1	49.7	49 ± 1
28.66	77.34	31.1	29 ± 1	60.9	61 ± 1

Mixtures of the enantiomers of **2b** and of **8** were prepared from racemic and dextrorotatory material. The melting behaviour of these mixtures is shown in *Fig. 1A* and *1B*, respectively, the data are given in *Table 2* and *3*. The melting diagrams of the mixtures of enantiomers were measured in order to verify that the mixtures exhibit a normal behaviour (no solid solutions!).

D) X-Ray Crystal Structure Analysis of 2f. – Monoclinic, $a = 6.660(1)$, $b = 9.329(3)$, $c = 29.759(9)$ Å, $\beta = 99.1°(2)$, $V = 1826$ Å^3, $Z = 4$, $C_{16}H_{21}F_3O_6$, space group $P2_1$, $d_x = 1.33$ g·cm^{-3}. Crystal structure analysis of **2f**: 3089 independent reflexions (2772 with $I > 3\sigma(I)$) were measured with an *Enraf-Nonius CAD 4* diffractometer at r.t. out to sin $\theta/\lambda \leq 0.6$ Å^{-1} (MoK_α radiation, $\lambda = 0.71069$ Å). The structure was solved by direct methods [31] and refined by full-matrix least-squares analysis [32] [33]. All H-atoms except those from the ethyl ester groups were located in a difference synthesis. The refinement with a modified weighting scheme [34] with $r = 6$ Å^2 converged with $R = 0.050$ ($R_w = 0.047$)[13]).

Note Added in Proof. – After this paper had been submitted, *Wynberg & Staring* published [1b] new results which prove that their previous assignment [1a] of the absolute configuration of (−)-**1b** has to be reversed. The correlation of configuration of our product (−)-**1b** is based on this revised assignment. The correction has been made at the galley-proof stage.

[13]) Atomic coordinates have been deposited with the *Cambridge Crystallographic Data Centre*, Lensfield Road, Cambridge, England.

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