(*R*)-Ethyl 4-*t*-Butoxy-3-hydroxybutanoate, a Versatile Chiral Building Block for EPC (Enantiomerically Pure Compound) Syntheses, by Yeast Reduction of Ethyl 4-*t*-Butoxy-3-oxobutanoate

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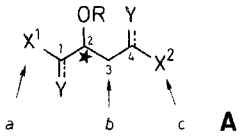
Reduction of ethyl 4-*t*-butoxy-3-oxobutanoate with fermenting yeast yields (*R*)-ethyl 4-*t*-butoxy-3-hydroxybutanoate in 97% e.e. Since the protective group is readily removed from the product of reduction, the present procedure provides a simple entry to the "world of chiral blocks" formally derived from (*R*)-malic acid.

Malic acid is a useful chiral starting material for syntheses of natural products and of biologically active compounds. This is due to its functionality pattern (see **A**) and to the fact that it is available in enantiomerically pure form[2]. Thus, depending on the type of protection and on the oxidation state of the two terminal centers of the C_4-chain, the carbon skeleton can be elaborated[3] at both ends (*a*)[4] and (*c*)[4,5], as well as at carbon-3 (*b*)[6,7,8].



A

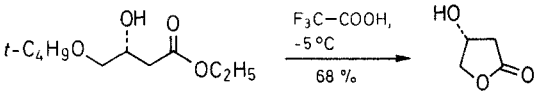
Y = O, H/OR, H_2

X^1, X^2 = OH, OR, halogen, H

In order to do this, however, it is necessary to differentiate the two carboxylic groups of malic acid and this is possible by various chemical[9] and biochemical[10] methods. It is also important to note that, while (*S*)- or natural malic acid is inexpensive, the (*R*)-enantiomer is not, and is usually made from (*R,R*)-tartaric acid[2,11]. We have now found a direct preparative access to a suitably protected 3,4-dihydroxybutanoate which is formally derived from (*R*)-malic acid.

We used the enantioselective reduction of an acetoacetic acid ester by fermenting baker's yeast[12], a method which was first demonstrated for the parent compound by Friedmann[13] in 1931, and which was recently applied to several 4-heterosubstituted derivatives[14]. Our substrates **1** were prepared from 4-chloro-3-oxo butanoates[15]. The ethyl *t*-butoxy ester **1a** was reduced[16] with the greatest selectivity, as determined by ^{19}F-N.M.R. spectroscopy of *Mosher*'s MTPA esters[17] derived from **2a–c**, as well as by recrystallization[18] of the 3,5-dinitrobenzoate of **2a** to constant specific rotation.

The sense of chirality (*R*) of the major enantiomer **2a** was established by chemical correlation: *t*-butyl ether cleavage in trifluoroacetic acid at -5°C and acid-catalyzed lactonization produced dextrorotatory **3** in 68% yield with an $[\alpha]_D$ value of 94°, which compares with literature values of $+77$° and -86° for samples prepared from (*R*)-(+)-[19] and (*S*)-(−)-malic acid[9], respectively.

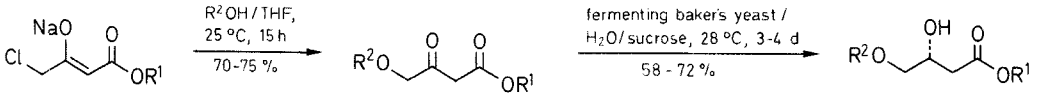


2a **3**

Assuming that a *t*-butoxy group is larger than a methoxycarbonyl and an ethoxycarbonyl group, and following Prelog's rule[20], one might have had expected the opposite stereochemical course of the reduction – note also the increase in selectivity[12,14] from 91:9 to 98.5:1.5 on going from the methyl ester **1b** to the ethyl ester **1a**.

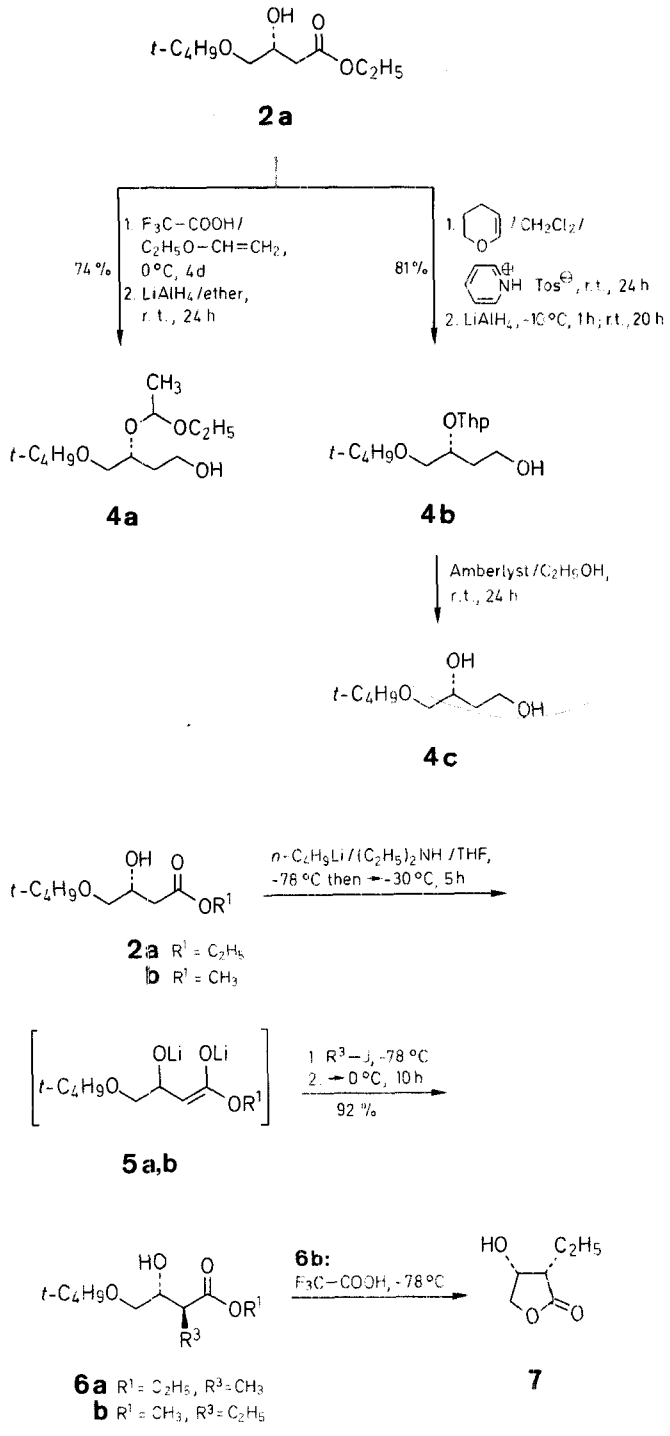
The presence of the *t*-butoxy group in **2a** allows for a more versatile and simpler strategy of protection of the three functional groups in the present C_4-building block, as compared with the access from malic acid[2,21]. Thus, the hydroxy group of **2a** can be protected by reaction with ethyl vinyl ether or with dihydropyran, so that subsequent lithium aluminium hydride reduction leads to derivatives (**4a** and **4b**, respectively) of 1,2,4-butanetriol with two different protecting groups in the 1- and 2-positions and a free 4-hydroxy group. Cleavage of the tetrahydropyranyl group from **4b** furnishes the triol mono-protected[22] in the 1-position (**4c**).

Finally, we have methylated and ethylated the *t*-butoxy-hydroxy esters **2a** and **2b** through alkoxide enolates[6,23,24], see **5**. These reactions lead predominantly (> 80% d.s.) to the products **6** of *u*-configuration[25], similar to the reactions of dilithiated malic esters and other β-hydroxy esters (see the experimental section). This was proved by conversion of the alkylation product **6b** to the known hydroxy-ethyl-lactone **7**.



1a-c **2a-c**

1, 2	R^1	R^2	1	2		
			Yield [%]	Yield [%]	$[\alpha]_D$	e.e. [%]
a	C_2H_5	*t*-C_4H_9	75	72	+12.8°	97
b	CH_3	*t*-C_4H_9	75	70	+10.3°	82
c	C_2H_5	$C_6H_5CH_2$	70	58	+6.3°	56



The present procedure brings about a substantial improvement for entry into the (*R*)-malic acid manifold of enantiomerically pure compound (EPC) syntheses[2,26].

Optical rotations were measured on a Perkin-Elmer 241 polarimeter; concentrations are reported in g/100 ml of solvent. I. R. spectra were recorded using neat films between NaCl plates on a Perkin Elmer 297 spectrophotometer unless otherwise noted. Mass spectra were obtained on a Hitachi-Perkin-Elmer RMU-6M spectrometer. The ^{1}H-N.M.R. (90 MHz unless otherwise noted) and the ^{19}F-N.M.R. (94 MHz) spectra were recorded using $CDCl_3$ solutions on a Varian EM-390 and a Varian XL-100 spectrometer. Capillary gas chromatograms were measured on a Carlo Erba Fractovap (20 m Pluronic L-64 column). Melting and boiling points are uncorrected.

The following procedures describe only the preparation and subsequent conversions of the dihydroxybutanoic acid derivative **2a** which was formed with the highest e.e. of the studied compounds. Spectroscopic data and additional information about the other compounds mentioned in the text above but not described in this experimental section can be requested from the correspondence author, see also Ref.[1].

Ethyl 4-*t*-Butoxy-3-oxobutanoate (1a):
To a stirred suspension of sodium hydride (4.8 g, 0.20 mol) and potassium *t*-butoxide (22.4 g, 0.20 mol) in tetrahydrofuran (300 ml) ethyl 4-chloro-3-oxo butanoate (30 g, 0.18 mol) is added; the temperature is not allowed to rise above 40 °C. After 20 h at room temperature, the brownish suspension is acidified by pouring into a mixture of ice (100 ml) and concentrated hydrochloric acid (50 ml). The product is extracted with ether (3 × 100 ml). The combined ether extracts are washed with brine (50 ml), dried with magnesium sulfate, evaporated, and distilled, giving **1a** as a slightly yellow colored oil; yield: 27.6 g (75%); b.p. 78–80 °C/1 torr.

^{1}H-N.M.R.: δ = 4.2 (q, J = 7 Hz, 2H, OCH_2CH_3); 4.0 [s, 2H, $CH_2OC(CH_3)_3$]; 3.5 (s, 2H, $COCH_2CO$); 1.2 (*t*, J = 7 Hz, 3H, CH_3); 1.1 ppm [s, 9 Hz, $C(CH_3)_3$].

(*R*)-Ethyl 4-*t*-Butoxy-3-hydroxybutanoate (2a):
Fresh baker's yeast (1000 g) is dispersed at about 28 °C in a solution of saccharose (1000 g) in tap water (8 l). After 0.5 h ethyl ester **1a** (35 g, 0.17 mol) is added over 10 h. The dispersion is allowed to stirr for 4 days at 28 °C until no more starting material remains (capillary G.C.). After centrifugation, the aqueous phase is extracted with ether (1000 ml) for 24 h. Drying with magnesium sulfate, evaporating, and distilling (Vigreux column, 10 cm) gives **2a**; yield: 24.7 g (70%); b.p. 80–82 °C/0.1 torr; $[\alpha]_D$: + 12.8° (*c* 1.5, $CHCl_3$).

$C_{10}H_{20}O_4$	calc.	C 58.80	H 9.87
(202.3)	found	58.57	9.93

M.S.: *m/e* = 131 (25); 118 (36); 117 (77); 85 (28); 71 (38); 57 (100).

I. R.: ν = 3450 (br. s); 2970 (s); 2930 (s); 2875 (m); 1720 (s); 1365 (m); 1175 (s); 1080 (s); 1020 (m); 880 (m) cm^{-1}.

^{1}H-N.M.R.: δ = 4.2 (q, J = 7 Hz, 2H, OCH_2CH_3); 4.1 (m, 1H, CHOH); 3.4–3.3 [m, 2H, $CH_2OC(CH_3)_3$]; 2.9 (br. s, 1H, OH); 2.6–2.5 (m, 2H, $CH_2COOC_2H_5$); 1.3 (t, J = 7 Hz, 2H, OCH_2CH_3), 1.2 ppm [s, 9H, $C(CH_3)_3$].

(R)-α-Methoxy-α-trifluoromethylphenylacetic (MTPA) Ester of 2a:
To a stirred solution of (*R*)-α-methoxy-α-trifluoromethyl phenylacetic acid chloride in a solvent mixture of pyridine/carbon tetrachloride (0.6 ml; 1/1), compound **2a** (20 µl) is added. After 12 h, 3-dimethylamino-1-propylamine (25 µl) is injected. The resulting solution is stirred for 5 min, taken up in ether (20 ml), and subsequently washed with 2 normal hydrochloric acid, saturated sodium carbonate solution, and brine. Drying with magnesium sulfate and evaporating gives a colorless oil.

^{19}F-N.M.R. ($CDCl_3/CF_3COOH$): δ = − 71.49 (0.27); − 71.52 ppm (20.00); corresponding to an e.e. of 97%.

3,5-Dinitrobenzoate of 2a:
At 0 °C, ethyl (*R*)-4-*t*-butoxy-3-hydroxybutanoate (2.0 g, 9.8 mmol) is added to a solution of 3,5-dinitrobenzoyl chloride (2.4 g, 0.3 mmol) in pyridine (8 ml). After 10 h, the mixture is poured onto ice (50 ml) and extracted with ether (3 × 20 ml). Washing of the combined extracts with 2 normal hydrochloric acid, saturated sodium hydrogen carbonate solution, and brine, drying with magnesium sulfate, and evaporating affords yellowish crystals of the crude ester; yield: 3.7 g (95%); $[\alpha]_D$: + 19.0° (*c* 1.0, $CHCl_3$). The crude 3,5-dinitroester is recrystallized from chloroform/hexane to constant specific rotation (one or two recrystallizations); yield: 2.2 g (53%); $[\alpha]_D$: + 20.1° (*c* 1.5, $CHCl_3$); m.p. 59–60 °C.

$C_{17}H_{22}N_2O_9$:	calc.	C 51.26	H 5.57	N 7.03
(398.4)	found	51.25	5.54	7.05

M.S.: *m/e* = 325 (10); 195 (21); 149 (12); 130 (25); 111 (16); 85 (30); 75 (17); 57 (100).

I. R. (KBr): ν = 3100 (w); 2970 (m), 1730 (s), 1540 (s), 1345 (s), 1275 (s), 1095 (m), 1075 (m), 1065 (m) cm^{-1}.

^{1}H-N.M.R.: δ = 9.3–9.2 (m, 3 H_{arom}); 5.8–5.5 (m, 1H, CHOCO) 4.2 (q, J = 7 Hz, 2H, OCH_2CH_3); 3.7 [d, J = 5 Hz, 2H $CH_2OC(CH_3)_3$]; 2.9 (d, J = 7 Hz, 2H, CHCOOEt); 1.3 (t J = 7 Hz, 3H, CH_3); 1.2 ppm [s, 9H, $C(CH_3)_3$].

Hydrolysis of the 3,5-Dinitrobenzoate of 2a:
The 3,5-dinitrobenzoate of **2a** (2.0 g, 5.0 mmol) and tetraethyl titanate (0.3 g, 1.3 mmol) are refluxed in ethanol (30 ml) for 20 h. After cooling to room temperature, the solution is evaporated to about 15 ml and filtered from ethyl 3,5-dinitrobenzoate. Flash chromatography on silica gel with ether/pentane (1:1) gives optically pure **2a**; yield: 0.93 g (91%); $[\alpha]_D$: +13.2° (*c* 1.5, $CHCl_3$).

(*R*)-3-Hydroxytetrahydrofuranone (3):
Compound **2a** (6.0 g, 29.4 mmol) is added under an inert atmosphere (argon) to trifluoroacetic acid (20 ml) at −10°C. After 2 h at −10° to −5°C, ice-cooled toluene (20 ml) is injected, and the mixture of solvents is stripped off (at 10°C). The yellow residue is dissolved in dichloromethane (40 ml) and silica gel (2 g) is added. After 36 h, the mixture is filtered, evaporated, and distilled. After a forerun (elimination product), compound **3** is obtained as a viscous oil; yield: 2.0 g (68%); b.p. 90–95°C/0.1 torr; $[\alpha]_D$: +94° (*c* 1.5, C_2H_5OH).

M.S.: *m/e* = 102 (M^+).

(*R*)-3-(1-Ethoxyethoxy)-4-*t*-butoxybutanol (4a):
At 0°C a catalytic amount of trifluoroacetic acid is added to a mixture of **2a** (2.0 g, 9.8 mmol) and ethyl vinyl ether (1.1 g, 15 mmol). After 4 days the mixture is neutralized with sodium hydrogen carbonate, filtered, and evaporated. The crude product is dissolved in ether (10 ml) and injected into a suspension of lithium aluminum hydride (1 g, 26 mmol) in ether (100 ml). After stirring for 24 h at room temperature, the excess lithium aluminum hydride is hydrolyzed by adding successively ethyl acetate and water. Extraction with dichloromethane (4 × 30 ml), drying with magnesium sulfate, evaporation and finally flash chromatography with pentane/ether (3:1) affords the product **4a**; yield: 1.70 g (74%).

$C_{12}H_{26}O_4$	calc.	C 61.51	H 11.18
(234.3)	found	61.77	11.40

M.S.: *m/e* = 132 (10); 15 (10); 101 (93); 71 (42); 59 (35); 57 (100).

I.R.: *v* = 3400 (br., m); 2970 (s); 2930 (m); 1380 (m); 1360 (m); 1105 (s); 1075 (s); 1050 (s); 995 (m).

^{1}H-N.M.R.: *δ* = 3.8 (q, *J* = 6 Hz, 1 H, OCHO); 3.8-3.2 (m, 8 H); 1.9-1.7 (m, 2 H); 1.3 (t, *J* = 7 Hz, 3 H, CH_2CH_3); 1.2 (d, *J* = 7 Hz, 3 H, $CHCH_3$); 1.2 ppm [s, 9 H, $C(C_3)_3$].

(*R*)-4-*t*-Butoxy-3-tetrahydropyranoyl-1,3-butanediol (4b):
To a solution of **2a** (2.0 g, 9.8 mmol) and dihydropyran (2.0 g, 23.8 mmol) in dichloromethane (10 ml) is added pyridinium *p*-toluenesulfonate (0.05 g). After 24 h, the organic phase is washed with saturated sodium hydrogen carbonate solution, dried with magnesium sulfate, and evaporated. The crude residue is dissolved in tetrahydrofuran (10 ml) and added at −10°C to a suspension of lithium aluminum hydride (0.8 g, 21 mmol) in tetrahydrofuran (20 ml) over 1 h. After 20 h at room temperature, the mixture is worked-up in the same manner as described for **4a**; yield: 1.95 g (81%).

$C_{13}H_{26}O_4$	calc.	C 63.38	H 10.64
(246.4)	found	63.53	10.48

M.S.: *m/e* = 159 (2); 85 (100); 84 (12); 75 (12); 71 (14); 57 (70).

I.R.: *v* = 3450 (br. m); 2970 (m); 2930 (m); 2870 (m); 1360 (m); 1195 (m); 1135 (m); 1115 (m); 1075 (s); 1020 (s) cm^{-1}.

^{1}H-N.M.R.: *δ* = 4.7 (br. s, 1 H, OCHO); 4.1–3.2 (m, 8 H); 1.9–1.4 (m, 8 H); 1.2 ppm [s, 9 H, $C(CH_3)_3$].

(*R*)-4-*t*-Butoxy-1,3-butanediol (4c):
To a solution of **4b** (2.0 g, 8.1 mmol) in ethanol (10 ml), Amberlyst® 15 (0.2 g) is added. After 24 h at room temperature, the mixture is filtered, evaporated, and purified by bulb-to-bulb distillation; yield: 1.2 g (92%); b.p. 110–115°C (oven temperature)/0.5 torr; $[\alpha]_D$: −0.6° (*c* 2.0, $CHCl_3$).

$C_8H_{18}O_3$	calc.	C 59.23	H 11.18
(162.2)	found	59.03	11.40

M.S.: *m/e* = 106 (2); 87 (6); 75 (41); 59 (20); 57 (100).

I.R.: *v* = 3380 (br. s); 2970 (s); 2930 (m); 2870 (m); 1360 (m); 1195 (m); 1080 (s) cm^{-1}.

^{1}H-N.M.R. (300 MHz): *δ* = 3.85–3.81 (m, 1 H, CHOH); 3.72 [t, *J* = 6 Hz, 2 H, $CH_2OC(CH_3)_3$]; 3.39–3.30 (br., 2 H, OH); 3.28 (dd, *J* = 9 Hz, 4 Hz, 1 H, CH_2OH); 3.20 (dd, *J* = 9 Hz, 7 Hz, 1 H, CH_2OH); 1.65–1.59 (m, 2 H, $CHCH_2CH_2$); 1.12 ppm [s, 9 H, $C(CH_3)_3$].

(2*S*,3*R*)-Ethyl 4-*t*-Butoxy-2-methyl-3-hydroxybutanoate (6a):
At −78°C, *n*-butyllithium (12.7 ml hexane solution, 20 mmol) is added by syringe to a solution of diethylamine (3.1 ml, 22 mmol) in tetrahydrofuran (50 ml) under an argon atmosphere. After 10 min at 0°C, hydroxy ester **2a** (2.04 g, 10 mmol) is added at −78°C. The solution is allowed to warm to −30°C over 5 h, recooled to −78°C and methyl iodide (1.25 ml, 20 mmol) is injected. The mixture is allowed to warm to 0°C within 10 h and is then hydrolyzed by pouring into ice (30 ml). The solution is acidified with 2 normal hydrochloric acid (20 ml) and extracted with ether (3 × 30 ml). Washing of the extracts with brine, drying with magnesium sulfate, evaporating, and bulb-to-bulb distillation gives a mixture of diastereomers (2*S*,3*R*), (2*R*,3*R*) in a ratio of 82:18 (capillary G.C.); yield: 2.0 g (92%); b.p. 110–120°C (oven temperature)/0.1 torr.

$C_{11}H_{22}O_4$	calc.	C 60.52	H 10.16
(218.3)	found	60.29	10.28

M.S.: *m/e* = 161 (3); 145 (18); 131 (86); 117 (71); 99 (20); 85 (57); 57 (100).

I.R.: *v* = 3460 (br. m); 2970 (s); 2930 (m); 2870 (w); 1720 (s); 1460 (m); 1365 (m); 1190 (s); 1035 (s); 1050 (m); 1020 (m) cm^{-1}.

^{1}H-N.M.R.: *δ* = 4.2 (q, *J* = 7 Hz, 2 H, OCH_2CH_3); 3.9-3.7 (m, 1 H, CHOH); 3.6-3.4 [m, 2 H, $CH_2OC(CH_3)_3$]; 3.0 (d, *J* = 6 Hz, 1 H, OH); 2.8-2.5 (m, 1 H, $CHCH_3$); 1.3 (t, *J* = 7 Hz, OCH_2CH_3); 1.2 (d, *J* = 7 Hz, 3 H, $CHCH_3$); 1.2 ppm [s, 9 H, $C(CH_3)_3$].

Alkylation of 2b to 6b and Conversion to the Lactone 7:
Following exactly the same procedure as for the methylation of **2a** to **6a**, **2b** (82% e.e.) is ethylated, yield of **6b**: 92%; diastereomeric ratio (2*S*,3*R*): (2*R*,3*R*) = 92:8; $[\alpha]_D$: +11.2° (*c* 1.5, $CHCl_3$) of the main isomer.

A sample of **6b** (92% d.s., 82% e.e.) is deprotected and cyclized to the lactone **7** as described above for the conversion of **2a** to **3**; yield: 40%. Comparison of ^{1}H-N.M.R. and ^{13}C-N.M.R. spectra with literature data[8] proved the *cis*-configuration of the lactone **7**.

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