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Synthesis and lipase-catalyzed asymmetric acetylation of 3-hydroxy-2-hydroxymethylpropanal acetals

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Abstract: Prochiral dialkylacetal derivatives of 3-hydroxy-2-hydroxymethylpropanal **6a–e** were synthesized from the corresponding 2-substituted diethyl malonates **5a–e** and subjected to asymmetric enzymatic acetylation. The diethyl malonates **5a–f** were prepared from diethyl chloromethylenemalonate **3** by using either a one- or a two-step process. Asymmetric acetylation of 3-hydroxy-2-hydroxymethylpropanal diethyl acetal **6b** with several enzymes was studied first, showing the highest enantiotopic selectivity with lipase from *Pseudomonas fluorescens* (PfL). Solvent effect was also investigated: the best selectivity was obtained in a mixture of hexane and diethyl ether. Furthermore, several other acetals **6a–e** were also tested under the optimal acetylation conditions. © 1997 Elsevier Science Ltd. All rights reserved.

Optically active C_3 building blocks are of continuously raising interest both in the manufacture of commercial products and in the research of biochemical processes. Products arising from asymmetric functionalization of 3-hydroxy-2-hydroxymethylpropanal dialkylacetals **6a–e** can be favorably used as multifunctional building blocks due to their three sites of different reactivity.

Diethyl ethoxymethylenemalonate **1** is a commercially available compound and can be converted to the desired acetals **6a–e** conveniently in reaction sequences which manifest sometimes unexpected behaviour (Scheme 1). Since charge distribution on the α- and β-carbon centers adjacent to the ether oxygen atom in the vinyl ether type compound diethyl ethoxymethylenemalonate **1** is opposite to the normal vinyl ethers, preparation of diethyl formylmalonate by the generally applied acid-catalyzed methods failed. The desired reaction, however, could be carried out in aqueous NaOH solution[1] smoothly. Diethyl formylmalonate exists, in accordance with previous results, exclusively in its enolic form (i.e. diethyl hydroxymethylenemalonate, **2**. The close similarity of charge distribution on C_1 and C_2 of this enolic compound **2** to those of its parent vinyl ether **1** may also rationalize why traditional acid-catalyzed acetal formation cannot be applied for further transformations. Diethyl ethoxymethylenemalonate **1**, however, can be directly converted into diethyl (diethoxy)methylmalonate **5b** under basic conditions, e.g. by using sodium ethylate[2,3] or sodium[4] in ethanol. Similarly, diethyl ethoxymethylenemalonate **1** was transformed into the corresponding dimethylacetal dimethylester by base-catalyzed reaction in methanol.[5] Since general methods for the preparation of further acetals were needed, we have chosen the known diethyl chloromethylenemalonate **3**[6], obtained from diethyl hydroxymethylenemalonate **2** by a significantly improved method using thionyl chloride, as a common precursor. A report on transformation of this chloromethylene derivative **3** with an alcohol in the presence of pyridine to the corresponding diethyl alkoxymethylenemalonate[7] prompted us to prepare a series of such alkoxymethylene compounds **4a–h** from which a mild base-catalyzed alkoxide addition yielded the desired acetals **5a–e** smoothly. Bulkiness of the alcohol seems to play a crucial role in these

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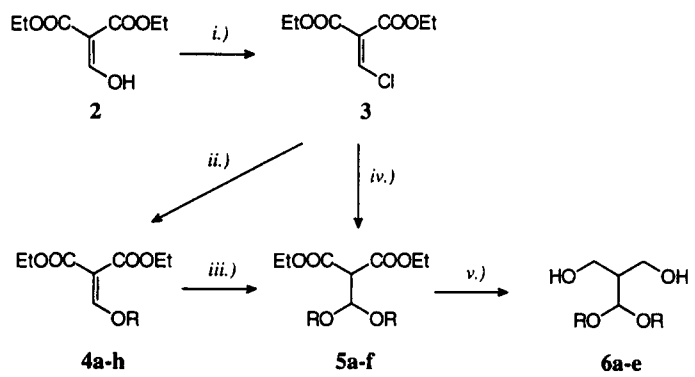
addition reactions: *iso*-propoxide-, *tert*-butoxide- and phenoxide-addition cannot be accomplished. Attempted preparation of methyl–phenyl or methyl–isopropyl acetals was also unsuccessful either from diethyl methoxymethylenemalonate **4a** or from diethyl (*iso*-propyloxy)methylenemalonate **4g** or diethyl phenoxymethylenemalonate **4h** with the corresponding alcohol. Alternatively, acetals **5a–e** can be obtained directly from diethyl chloromethylenemalonate **3** in a one-pot reaction by using a slight excess (1.1–1.3 equiv.) of sodium hydride in the corresponding alcohol. Cyclic acetal **5c**, however, could only be prepared by the one-pot method. Reduction of diester acetals **5a–e** by lithium aluminum hydride yielded the acetal derivatives of 3-hydroxy-2-hydroxymethylpropanal **6a–e**. Unfortunately, the diallyl acetal **5f** decomposed during this reduction.



4-6	R
a	$-CH_3$
b	$-CH_2CH_3$
c	$-CH_2CH_2-$
d	$-CH_2C_6H_5$
e	$-CH_2CH_2CH(CH_3)_2$
f	$-CH_2CH=CH_2$
g	$-CH(CH_3)_2$
h	$-C_6H_5$

Reagents: *i.)* $SOCl_2$, DMF; *ii).* ROH, pyridine; *iii.)* ROH, cat. Na; *iv.)* ROH, 1.3 equiv. NaH; *v.)* $LiAlH_4$.

R	Reaction *iii.)* **4**, Yield %	Reaction *iv.)* **5**, Yield %	Reaction *v.)* **5**, Yield %	Reaction *vi.)* **6**, Yield %
a, methyl-	95	87	92	86
b, ethyl	96	90	93	92
c, 1,2-ethenyl-	-	-	94	37
d, benzyl-	95	80	80	82
e, *i*-amyl-	95	86	89	74
f, allyl-	94	85	77	decomposition
g, *i*-propyl-	95	no reaction	no reaction	-
h, phenyl-	91	no reaction	no reaction	-

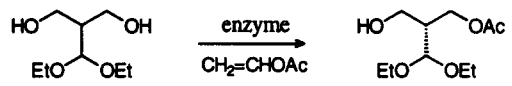
Scheme 1. Preparation of 3-hydroxy-2-hydroxymethylpropanal acetals **6a–e**.

After having the desired prochiral diols **6a–e** in our hands, first we tested the asymmetric acetylation of 3-hydroxy-2-hydroxymethylpropanal diethylacetal **6b** with vinyl acetate in hexane using various enzymes (Table 1).

Since the highest selectivity was achieved with PfL, this enzyme was chosen for further studies. Next, the solvent effect on enantiotopic selectivity of this PfL-catalyzed acetylation was investigated (Table 2).

Interestingly, no correlation between the polarity of the solvent and the enantiotopic selectivity of the enzyme was found. Trace water content of the solvent also seems to have no significant influence on the selectivity, and in the protic *tert*-butanol no reaction occurred. Since the best enantiotopic

Table 1. Acetylation of 3-hydroxy-2-hydroxymethylpropanal diethylacetal **6b** with various enzymes



6b **7b**

Enzyme[a] (mg)	Time[b] (h)	Yield (%)	ee[c] (%)
PfL (10)	8	71.7	66
PPL (30)	120	78.2	17
CcL (30)	120	74.9	57
PLE (50)	120	75.5	52
MjL (10)	170	-	-
RaL (10)	170	-	-
Lipase-PS (10)	8	66	60
Lipase-AK (10)	8	57	57

[a] PfL: lipase from *Pseudomonas fluorescens*, PPL: lipase from porcine pancreas, CcL: lipase from *Candida cylindracea*, PLE: pig liver acetone powder, MjL: lipase from *Mucor javonicus*, RaL: lipase from *Rhisopus arrhisus*; [b] 200 mg of acetal **6b** was stirred with the enzyme in vinyl acetate (2 ml) at RT; [c] Enantiomeric excess values were determined by using ^{1}H-NMR spectra of (*S*)-MTPA-ester of **7b**.

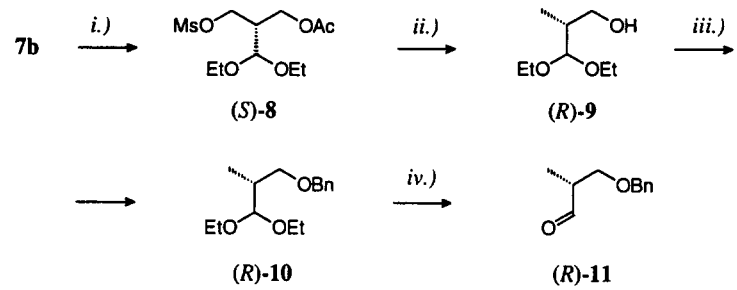
Table 2. Acetylation of 3-hydroxy-2-hydroxymethylpropanal diethylacetal **6b** by PfL in various solvents

Solvent	Time[a] (h)	Yield (%)	ee (%)
hexane	10	95	68
hexane : Et_2O (1 : 1)	10	85	71
hexane : $(i\text{-}Pr)_2O$ (1 : 1)	10	93	69
CCl_4	10	90	48
toluene	20	94	68
tetrahydrofuran	20	69	62
acetonitrile	20	84	69
t-butanol	10	-	-
hexane : $(i\text{-}Pr_2O)$: H_2O (1 : 1 : 0.002)	20	83	69

[a] **6b** (200 mg) and PfL (10 mg) were stirred in the given solvent (2 ml) and vinyl acetate (0.25 ml)

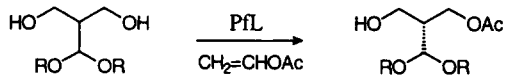
selectivity was achieved in the mixture of hexane and diethyl ether, this solvent mixture was applied in the further studies.

After studying the factors influencing the enantiotopic selectivity of acetylation of the prochiral diol **6b**, absolute configuration of the monoacetate product **7b** was determined by chemical correlation (Scheme 2). The reaction sequence leading to the known (*R*)-(−)-3-benzyloxy-2-methylpropanal (*R*)-**11**[8,9], *via* mesylation, reduction of the mesylate, benzylation and hydrolysis, starting from the monoacetate **7b** proved its (*R*)-configuration.



Scheme 2. Determination of the absolute configuration of the optically active monoacetate **7b**. Reagents: *i.)* MsCl, Et_3N; *ii.)* $LiAlH_4$; *iii.)* BnCl, NaH; *iv.)* cat. HCl, $AcOH–H_2O$.

Table 3. Acetylation of prochiral diols having various acetal-type substituents **6a–d**



6a-d **7a-d**

R	Time [a] (h)	Yield (%)	$[\alpha]_D$ [b]	$[\alpha]_D^{100\%}$ [b, c]	ee (%)
a, methyl-	12	46	+4.1	+9.4	44 [d]
b, ethyl-	10	85	+4.9	+7.0	71
c, 1,2-ethenyl-	7	38	+0.3	-	~0
d, benzyl-	21	92	+7.4	+10.5	70 [d]
e, *i*-amyl-	24	70	+3.7	+5.5	68 [d]

[a] 200 mg of **6a-e**, PfL (10 mg), and vinyl acetate (0,25 ml) in hexane:diethyl ether 1:1 (2 ml) was stirred at RT; [b] c=1, acetone; [c] extrapolated values calculated from specific rotation of **6a-e** and from the corresponding enantiomeric excess values obtained from ^{1}H-NMR spectra of MTPA-esters of the monoacetates; [d] absolute configuration is assumed to be (*R*) by analogy with that of **7b**.

Finally, several prochiral diols with acetal-type 2-substituents **6a–e** were acetylated using PfL under the optimum conditions (Table 3). Within this series, (*R*)-configuration was assigned to all optically active products **7a,b,d,e**, based on the analogous manner of the enzymatic acetylations and on the same signs of the specific rotations of the products. The lipase-catalyzed reaction yielding monoacetate **7b** with e.e. of 71% from the diethyl acetal **6b** proceeded with the highest enantiotopic selectivity. While di-*i*-amyl and dibenzyl acetals **6d,e** gave similarly good results (68 and 70% e.e., respectively), only a modest enantiotopic selectivity was found in acetylation of the dimethyl acetal **6a**, and almost racemic product **7c** was obtained from the cyclic acetal **6c**. The bulkiness of the acetal-type 2-substituent seems to be decisive for the enantiotopic selectivity: the small substituents gave poor results, the best selectivity was manifested with the medium-size diethyl acetal. Further increase of the bulkiness of the acetal moiety, however, did not increase the selectivity.

In summary, it may be concluded that the enzymatic acetylation of the prochiral 3-hydroxy-2-hydroxymethylpropanal acetals **6a–e** is a convenient method for the preparation of optically active acetals of 3-acetoxy-2-hydroxymethyl-propanal **7a–e**, which may serve as multifunctional chiral building blocks. The highest enantiotopic selectivities were obtained with diethyl and dibenzyl acetals, **6b** and **6e** respectively, using lipase from *Pseudomonas fluorescens* (PfL) and vinyl acetate in a mixture of hexane and diethyl ether. Among the optically active acetals **7a–e**, the dibenzyl acetal **7e**, whose

acetal moiety can be manipulated both by acid-catalysis and catalytic hydrogenation, may have the highest synthetic value.

Experimental

The ^{1}H-NMR spectra were recorded on a Bruker WM-250 spectrometer operating at 250 MHz. Enantiomeric excess values were determined by ^{1}H-NMR spectroscopy at 500 MHz on a Bruker DRX-500 spectrometer. All NMR spectra were measured in $CDCl_3$ solution and chemical shift values are expressed in ppm values from TMS as internal standard on the δ scale. IR spectra of thin film samples were taken on a Specord 2000 spectrometer. Optical rotations were determined on a Perkin Elmer 241 polarimeter. Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} alumina sheets applying hexane:acetone 10:4 mixture for elution. Spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution and heating of the dried plates. Preparative vacuum-chromatography[10] was performed using Merck Kieselgel 60 F_{254}. Porcine pancreatic lipase (PPL, Type II) was obtained from Sigma. Lipases from *Candida rugosa (cylindracea)* (CcL), *Pseudomonas fluorescens* (PfL), *Aspergillus niger* (AnL), *Mucor javonicus* (MjL), *Rhisopus arrhisus* (RaL), esterase from pig liver (PLE, acetone powder), diethyl ethoxymethylenemalonate, acetic anhydride, and vinyl acetate were products of Fluka. Lipase PS and Lipase AK were gifts from Amano. All solvents used were freshly distilled.

Diethyl chloromethylenemalonate 3

To a solution of diethyl hydroxymethylenemalonate (**2**, 29.4 g, 157 mmol) and N,N-dimethylformamide (0.5 ml) in toluene (200 ml) thionyl chloride (12.6 ml, 173 mmol) was added dropwise. The reaction mixture was heated under reflux until gas evolution ceased. After removal of the solvent by rotary evaporation, the residue was distilled *in vacuo* yielding 24.7 g (77%) of a colorless oil with characteristic odor. Bp: 64°C (0.2 Torr); *^{1}H-NMR*: 1.29 (t, 3H, CH_3), 1.34 (t, 3H, CH_3), 4.26 (q, 2H, OCH_2), 4.37 (q, 2H, OCH_2), 7.47 (s, 1H, =CH–Cl); *IR*: 3080, 2980, 1740, 1610, 1460, 1450, 1370, 1330, 1250, 1210, 1100, 1070, 1020, 910, 870, 840, 750 cm^{-1}; Calcd. for $C_8H_{11}O_4Cl$: C 46.50, H 5.37; found C 46.69, H 5.38.

*Preparation of diethyl alkoxymethylenemalonates **4a–h***

General procedure

Diethyl chloromethylenemalonate (**3**, 2.07 g, 10.0 mmol) and pyridine (1 ml) was added to the corresponding alcohol (20 ml) and the resulting solution was stirred at RT for 15 minutes. After removal of the excess alcohol by rotary evaporation, the residue was acidified with 5% HCl (10 ml) and extracted with dichloromethane (3×10 ml). The combined dichloromethane extracts were dried over Na_2SO_4 and concentrated in vacuum leaving a colorless oil which was purified by preparative vacuum-chromatography using hexane:acetone 10:1 as eluent.

*Diethyl methoxymethylenemalonate **4a***

Yield: 95%. *^{1}H-NMR*: 1.31 (t, 3H, CH_3), 1.36 (t, 3H, CH_3), 4.01 (s, 3H, OCH_3), 4.15–4.23 (m, 4H, 2 OCH_2), 7.55 (s, 1H, =CH–O); *IR*: 2980, 1730, 1640, 1450, 1400, 1380, 1280, 1210, 1140, 1090, 1020, 970, 860, 770 cm^{-1}; Calcd. for $C_9H_{14}O_5$: C 53.46, H 6.98; found C 53.26, H 6.96.

*Diethyl ethoxymethylenemalonate **4b***

Yield: 96%. *^{1}H-NMR* and *IR* spectra were in accordance with the literature[11].

*Diethyl benzyloxymethylenemalonate **4d***

Yield: 95%. *^{1}H-NMR*: 1.28 (t, 3H, CH_3), 1.33 (t, 3H, CH_3), 4.08–4.45 (m, 4H, 2 OCH_2), 4.69 (s, 2H, OCH_2Ph), 7.25–7.50 (m, 5H, ArH), 7.62 (s, 1H, =CH–O); *IR*: 3500 (br), 2980, 1730, 1630,

1500, 1460, 1370, 1290, 1150, 1090, 1020, 910, 860, 740, 700 cm^{-1}; Calcd. for $C_{15}H_{18}O_5$: C 64.74, H 6.52; found C 64.63, H 6.54.

Diethyl (i-amyloxy)methylenemalonate ***4e***

Yield: 95%. *^{1}H-NMR*: 0.94 (d, 6H, 2 CH_3), 1.30 (t, 3H, CH_3), 1.34 (t, 3H, CH_3), 1.30–1.79 (m, 3H, CH and CH_2), 4.10–4.43 (m, 6H, 3 OCH_2), 7.60 (s, 1H, =CH–O); *IR*: 2960, 1730, 1630, 1470, 1380, 1290, 1180, 1090, 1030, 960, 860, 800 cm^{-1}; Calcd. for $C_{13}H_{22}O_5$: C 60.45, H 8.58; found C 60.20, H 8.55.

Diethyl allyloxymethylenemalonate ***4f***

Yield: 94%. *^{1}H-NMR*: 1.30 (t, 3H, CH_3), 1.33 (t, 3H, CH_3), 4.18–4.40 (m, 4H, 2 OCH_2), 4.62 (mc, 2H, OCH_2), 5.37 (mc, 2H, $=CH_2$), 5.93 (mc, 1H, =CH–), 7.60 (s, 1H, =CH–O); *IR*: 2980, 1730, 1640, 1590, 1490, 1380, 1250, 1200, 1170, 1080, 1020, 760, 690 cm^{-1}; Calcd. for $C_{11}H_{16}O_5$: C 57.89, H 7.07; found C 58.10, H 7.09.

Diethyl (i-propyloxy)methylenemalonate ***4g***

Yield: 95%. *^{1}H-NMR*: 1.20–1.44 (m, 12H, 4 CH_3), 4.1–4.3 (m, 5H, 2 OCH_2, OCH), 7.66 (s, 1H, =CH–O); *IR*: 2980, 1730, 1630, 1470, 1450, 1380, 1290, 1250, 1190, 1140, 1100, 1030, 920, 850, 790 cm^{-1}; Calcd. for $C_{11}H_{18}O_5$: C 57.38, H 7.88; found C 57.62, H 7.90.

Diethyl phenyloxymethylenemalonate ***4h***

Yield: 91%. *^{1}H-NMR*: 1.31 (t, 3H, CH_3), 1.37 (t, 3H, CH_3), 4.20–4.43 (ms, 4H, 2 OCH_2), 7.10–7.48 (m, 5H, ArH), 7.89 (s, 1H, =CH–O); *IR*: 2980, 1730, 1630, 1470, 1450, 1370, 1280, 1240, 1180, 1090, 1030, 970, 940, 860, 770 cm^{-1}; Calcd. for $C_{14}H_{16}O_5$: C 63.63, H 6.10; found C 63.37, H 6.12.

Diethyl dialkoxymethylmalonates ***5a–f*** *from diethyl alkoxymethylenemalonates* ***4a–f***

General procedure

To a solution of diethyl alkoxymethylenemalonate (**4a–f**, 10 mmol) in the corresponding alcohol (ca. 5 mmol) catalytic amount (ca. 15 mg) of sodium was added and the resulting solution was stirred at 50°C for 30 minutes. After removal of the excess alcohol by rotary evaporator, 5% hydrochloric acid (5 ml) was added and the resulting mixture was extracted with chloroform (3×5 ml). The combined chloroform extracts were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue was purified by preparative vacuum-chromatography using hexane:acetone 10:1 as eluent resulting a colorless oil.

Diethyl dimethoxymethylmalonate ***5a***

Yield: 87%. *^{1}H-NMR*: 1.29 (t, 6H, 2 CH_3), 3.43 (s, 6H, 2 OCH_3), 3.74 (d, CH), 4.22 (q, 4H, 2 OCH_2), 5.00 (d, 1H, O–CH–O); *IR*: 2980, 2840, 1740, 1610, 1450, 1370, 1310, 1230, 1180, 1090, 1040, 950, 910, 860 cm^{-1}; Calcd. for $C_{10}H_{18}O_6$: C 51.27, H 7.75; found C 51.14, H 7.77.

Diethyl diethoxymethylmalonate ***5b***

Yield: 90%. *^{1}H-NMR* and *IR* spectra were in accordance with the literature.

Diethyl dibenzyloxymethylmalonate ***5d***

Yield: 80%. *^{1}H-NMR*: 1.23 (t, 6H, 2 OCH_3), 3.91 (d, 1H, CH), 4.18 (q, 4H, 2 OCH_2), 4.66 (dd, 4H, 2 OCH_2Ph), 5.40 (d, 1H, O–CH–O), 7.2–7.4 (m, 10H, Ar); *IR*: 3030, 2980, 2940, 1750, 1740, 1500, 1450, 1370, 1310, 1100, 1060, 1030, 910, 860, 740 cm^{-1}; Calcd. for $C_{22}H_{26}O_6$: C 68.38, H 6.78; found C 68.09, H 6.76.

Diethyl (di-i-amyloxy)methylmalonate ***5e***

Yield: 86%. *^{1}H-NMR*: 0.86 (d, 12H, 4 CH_3), 1.15–1.72 (m, 12H, 2 CH, 2 CH_3 and 2 CH_2), 3.45–3.78 (m, 5H, CH and 2 OCH_2), 4.18 (q, 4H, 2 OCH_2), 5.09 (d, 1H, O–CH–O); *IR*: 2960, 2870, 1740, 1640, 1470, 1370, 1310, 1180, 1140, 1100, 1070, 1030, 860 cm^{-1}; Calcd. for $C_{18}H_{34}O_6$: C 62.40, H 9.89; found C 62.28, H 6.43.

Diethyl diallyloxymethylmalonate ***5f***

Yield: 85%. *^{1}H-NMR*: 1.32 (t, 6H, $2CH_3$), 3.80 (m, 1H, CH), 4.07–4.35 (m, 8H, 4 OCH_2), 5.15–5.43 (m, 5H, 2 $=CH_2$ and O–CH–O), 5.90 (m, 2H, 2 =CH–); Calcd. for $C_{14}H_{22}O_6$: C 58.73, H 7.74; found C 58.84, H 7.71.

Diethyl dialkoxymethylmalonates ***5a–f*** *from diethyl chloromethylenemalonate* ***3***

General procedure

To a solution of diethyl chloromethylenemalonate (**3**, 3.1 g, 15.0 mmol) in the corresponding alcohol (15 ml) sodium hydride (0.48 g, 20.0 mmol) was added at 0°C and the resulting mixture was stirred for 30 minutes. After removal of the excess alcohol by rotary evaporator, the residue was neutralized by addition of 5% hydrochloric acid, diluted by water (10 ml) and extracted with chloroform (3×5 ml). The combined chloroform extracts were dried over Na_2SO_4 and concentrated. Usually, the product was used in the next reduction step as such. Analytical samples were purified by preparative vacuum-chromatography with hexane:acetone 10:1 as eluent.

Diethyl dialkoxymethylmalonates ***5a,b,d–f***

For yields: see table in Scheme 1; for analytical data: see the preceding section.

Diethyl (1,3-dioxolan-2-yl)malonate ***5c***

Yield: 94%. *^{1}H-NMR*: 1.27 (t, 6H, 2 CH_3), 3.68–3.83 (ms, 5H, CH and OCH_2–CH_2O), 4.21 (q, 4H, 2 OCH_2), 5.08 (d, 1H, O–CH–O); *IR*: 3650, 2970, 2840, 1740, 1730, 1620, 1450, 1440, 1370, 1300, 1230, 1180, 1170, 1080, 1040, 940, 920, 860, 750 cm^{-1}; Calcd. for $C_{10}H_{16}O_6$: C 51.72, H 6.94; found C 51.93, H 6.93.

Reduction of the diethyl dialkoxymethylmalonates ***5a–e***

General procedure

To a suspension of lithium aluminum hydride (0.95 g, 25 mmol) in dry tetrahydrofurane (30 ml) a solution of the diethyl dialkoxymethylmalonate (**5a–e**, 10.0 mmol) in dry tetrahydrofurane (10.0 ml) was added dropwise and the reaction mixture was heated under reflux for 1 hour. After cooling, the reaction mixture was quenched by careful addition of water (5 ml) and the resulting suspension was diluted with ethyl acetate (25 ml). The precipitate was filtered off and the filtrate was dried over Na_2SO_4 and concentrated by rotary evaporation. The residue was purified by preparative vacuum-chromatography with hexane:acetone 10:3 as eluent.

3-Hydroxy-2-hydroxymethylpropanal dimethyl acetal ***6a***

Yield: 86%. *^{1}H-NMR*: 2.03 (m, 1H, CH), 3.42 (s, 6H, 2 OCH_3), 3.77 (m, 4H, 2 OCH_2), 4.48 (d, 1H, O–CH–O); *IR*: 3400 (br), 2940, 2840, 1650, 1460, 1390, 1270, 1190, 1130 cm^{-1}; Calcd. for $C_6H_{14}O_4$: C 47.99, H 9.40; found C 48.16, H 9.43.

3-Hydroxy-2-hydroxymethylpropanal diethyl acetal ***6b***

Yield: 92%. *^{1}H-NMR*: 1.15 (t, 6H, 2 CH_3), 1.93 (m, 1H, CH), 3.46 and 3.67 (2 m, 4H, 2 OCH_2), 3.70 (m, 4H, 2 OCH_2), 4.54 (d, 1H, O–CH–O); *IR*: 3390 (br), 2940, 2850, 1650, 1450, 1380, 1270, 1190, 1130, 1060, 970 cm^{-1}; Calcd. for $C_8H_{18}O_4$: C 53.91, H 10.18; found C 53.80, H 10.15.

3-Hydroxy-2-hydroxymethylpropanal 1,2-ethenyl acetal ***6c***

Yield: 37%. *^{1}H-NMR*: 2.05 (m, 1H, CH), 3.75–4.03 (m, 8H, 4 OCH_2), 4.95 (d, 1H, O–CH–O); *IR*: 3380 (br), 2950, 2890, 1470, 1400, 1240, 1150, 1030, 950, 920 cm^{-1}; Calcd. for $C_6H_{12}O_4$: C 48.64, H 8.16; found C 48.75, H 8.18.

3-Hydroxy-2-hydroxymethylpropanal dibenzyl acetal ***6d***

Yield: 82%. *^{1}H-NMR*: 2.10 (m, 1H, CH), 3.77 (m(d), 4H, 2 OCH_2), 4.60 (dd, 4H, 2 OCH_2Ph), 4.81 (d, 1H, O–CH–O), 7.28 (m, 10H, ArH); *IR*: 3370, 3030, 2930, 2870, 1950, 1500, 1450, 1400, 1290, 1240, 1210, 1140, 1040, 930, 740, 700 cm^{-1}; Calcd. for $C_{18}H_{22}O_4$: C 71.50, H 7.33; found C 71.78, H 7.33.

*3-Hydroxy-2-hydroxymethylpropanal di-*i*-amyl acetal* ***6e***

Yield: 74%. *^{1}H-NMR*: 0.91 (d, 12H, $4CH_3$), 1.10–1.78 (m, 6H, 2 CH and 2 CH_2), 2.09 (m, 1H, CH), 3.39–3.80 (m, 8H, 4 OCH_2), 4.61 (d, 1H, O–CH–O); *IR*: 3370 (br), 2960, 2930, 2870, 1740, 1470, 1370, 1240, 1110, 1070, 800 cm^{-1}; Calcd. for $C_{14}H_{30}O_4$: C 64.09, H 11.52; found C 64.00, H 11.48.

Acetylation of 3-hydroxy-2-hydroxymethylpropanal diethyl acetal ***6b*** *with various enzymes*

General procedure

To a solution of 3-hydroxy-2-hydroxymethylpropanal diethyl acetal (**6b**, 200 mg) in vinyl acetate (2 ml) enzyme (for amount, see Table 1) was added and the resulting suspension was stirred at room temperature (for reaction time, see Table 1). After reaching a reasonable conversion the enzyme was filtered off and the filtrate was concentrated by rotary evaporator. The residue was subjected to column chromatography using hexane:acetone 5:1 as eluant yielding pure 3-acetoxy-2-hydroxymethylpropanal diethyl acetal **7b**. For yields and enantiomeric composition, see Table 1.

Acetylation of 3-hydroxy-2-hydroxymethylpropanal diethyl acetal ***6b*** *in various solvents*

General procedure: 3-Hydroxy-2-hydroxymethylpropanal diethyl acetal (**6b**, 200 mg), vinyl acetate (0.25 ml) and lipase from *Pseudomonas fluorescens* (10 mg) were added to the solvent (2 ml; for solvents, see Table 2) and the resulting suspension was stirred at room temperature. Work up of the products was carried out as described in the previous section. For reaction times, yields, and enantiomeric composition, see Table 2.

Acetylation of 3-hydroxy-2-hydroxymethylpropanal dialkyl acetals ***6a–e***

General procedure: 3-Hydroxy-2-hydroxymethylpropanal dialkyl acetal (**6a–e**, 200 mg), vinyl acetate (0.25 ml) and lipase from *Pseudomonas fluorescens* (10 mg) were added to a mixture of hexane and diethyl ether (1 ml, each) and the resulting suspension was stirred at room temperature. Work up of the product was carried out as described in the previous sections.

3-Acetoxy-2-hydroxymethylpropanal dimethyl acetal ***7a***

Yield: 46%. $[\alpha]_D$=+4.1, (c=1, acetone), e.e.%=44; *^{1}H-NMR*: 2.10 (s, 3H, CH_3), 2.16 (m, 1H, CH), 3.43 (s, 3H, .OCH_3), 3.47 (s, 3H, .OCH_3), 3.72 (m(d), 2H, OCH_2), 4.04–4.27 (m, 2H, $AcOCH_2$), 4.44 (d, 1H, O–CH–O); *IR*: 3465 (br), 2940, 2830, 1740, 1470, 1370, 1240, 1190, 1130, 1040, 980 cm^{-1}; Calcd. for $C_8H_{16}O_5$: C 49.99, H 8.39; found C 50.24, H 8.27.

3-Acetoxy-2-hydroxymethylpropanal diethyl acetal ***7b***

Yield: 85%. $[\alpha]_D$=+4.9, (c=1, acetone), e.e.%=71; *^{1}H-NMR*: 1.22 (t, 3H, CH_3), 1.23 (t, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.16 (m, 1H, CH), 3.51–3.57 (m, 2H, OCH_2), 3.67–3.80 (m, 4H, 2 OCH_2), 4.14 and 4.24 (2×dd, 2H, $AcOCH_2$), 4.58 (d, 1H, O–CH–O); *IR*: 3464 (br), 2980, 2930, 2900, 1740, 1450, 1370, 1240, 1110, 1060, 900 cm^{-1}; Calcd. for $C_{10}H_{20}O_5$: C 54.53, H 9.15; found C 54.22, H 9.31.

3-Acetoxy-2-hydroxymethylpropanal 1,2-ethenyl acetal 7c

Yield: 38%. $[\alpha]_D$=+0.3, (c=1, acetone); *^{1}H-NMR*: 2.08 (m, 1H, CH), 2.12 (s, 3H, CH_3), 3.73–4.15 (m, 6H, 3 OCH_2), 4.02–4.28 (m, 2H, $AcOCH_2$), 4.91 (d, 1H, O–CH–O); *IR*: 3450 (br), 2950, 2880, 1730, 1470, 1390, 1240, 1150, 1040 cm^{-1}; Calcd. for $C_8H_{14}O_5$: C 50.52, H 7.42; found C 50.71, H 7.69.

3-Acetoxy-2-hydroxymethylpropanal dibenzyl acetal 7d

Yield: 92%. $[\alpha]_D$=+7.4, (c=1, acetone), e.e.%=70; *^{1}H-NMR*: 1.92 (s, 3H, CH_3), 2.40 (m, 1H, CH), 3.74 (m, 2H, O–CH_2), 4.00–4.29 (m, 2H, $AcOCH_2$), 4.57 (dd, 4H, 2 OCH_2Ph), 4.71 (d, 1H, O–CH–O), 7.28 (m, 10H, ArH); *IR*: 3470 (br), 2960, 2930, 1740, 1460, 1370, 1230, 1040, 740 cm^{-1}; Calcd. for $C_{20}H_{24}O_5$: C 69.75, H 7.02; found C 70.01, H 7.19.

*3-Acetoxy-2-hydroxymethylpropanal di-*i*-amyl acetal 7e*

Yield: 70%. $[\alpha]_D$=+3.7, (c=1, acetone), e.e.%=68; *^{1}H-NMR*: 0.90 (d, 12H, 4 CH_3), 1.10–1.78 (m, 6H, 2 CH and 2CH_2), 2.04 (s, 3H, CH_3), 2.11 (m, 1H, CH), 3.41–3.83 (m, 6H, 3 OCH_2), 4.03–4.30 (m, 2H, $AcOCH_2$), 4.61 (d, 1H, O–CH–O); *IR*: 3470 (br), 2960, 2930, 2870, 1740, 1470, 1370, 1240, 1110, 1070, 830 cm^{-1}; Calcd. for $C_{16}H_{32}O_5$: C 63.13, H 10.59; found C 63.49, H 10.33.

*Determination of enantiomeric excess of 3-acetoxy-2-hydroxymethylpropanal dialkyl acetals **7a–e***

General procedure

To a solution of (*R*)-(−)-MTPA-Cl (38 mg, 0.15 mmol) in carbon tetrachloride (0.35 ml) 3-acetoxy-2-hydroxymethylpropanal dialkyl acetal (**7a–e**, 0.10 mmol; the corresponding racemic samples were obtained from **6a–e** by chemical acetylation using acetic anhydride and pyridine), pyridine (16 mg, 0.2 mmol), and N,N-dimethylaminopyridine (ca. 1 mg) were added and the resulting mixture was heated in a sealed ampoule at 50°C for 3 hours. The reaction mixture was washed with 5% hydrochloric acid (3×0.3 ml), the organic phase was dried over Na_2SO_4 and concentrated by rotary evaporator. The residue was analyzed by ^{1}H-NMR spectroscopy as such.

*Characteristic ^{1}H-NMR signals of **7a–e** MTPA-esters (diastereomeric mixtures from racemic monoacetates)*

(*R*)-**7a** MTPA ester: 3.997 (dd, 0.5 H); (*S*)-**7a** MTPA ester: 4.035 (dd, 0.5 H);
(*R*)-**7b** MTPA ester: 4.026 (dd, 0.5 H); (*S*)-**7b** MTPA ester: 4.059 (dd, 0.5 H);
(±)-**7c** MTPA ester: 2.015 (s, 1.5 H), 2.018 (s, 1.5 H);
(*R*)-**7d** MTPA ester: 4.062 (dd, 0.5 H); (*S*)-**7d** MTPA ester: 4.097 (dd, 0.5 H);
(*R*)-**7e** MTPA ester: 4.210 (dd, 0.5 H); (*S*)-**7e** MTPA ester: 4.213 (dd, 0.5 H);

*Determination of the configuration of 3-acetoxy-2-hydroxymethylpropanal diethyl acetal **7b***

*(S)-(+)-3-Acetoxy-2-methanesulfonyloxymethylpropanal diethyl acetal **8***

To a solution of 3-acetoxy-2-hydroxymethylpropanal diethyl acetal (**7b**, 5.12 g, 23.3 mmol; $[\alpha]_D$=+5.0, c=1, acetone), triethylamine (4.0 ml, 29 mmol) and 4-dimethylaminopyridine (50 mg) in dichloromethane (25 ml) a solution of methanesulfonyl chloride (2.2 ml, 28 mmol) in dichloromethane (20 ml) was added dropwise below 25°C and the resulting mixture was stirred at RT for 30 minutes. The reaction mixture was then washed with water (2×10 ml) and the organic layer was dried over Na_2SO_4 and concentrated by rotary evaporator yielding 6.7 g (23.4 mmol, 96%) of a colorless oil.

$[\alpha]_D$=+0.9, (c=1, acetone); *^{1}H-NMR*: 1.24 (t, 6H, 2CH_3), 2.10 (s, 3H, CH_3), 2.40 (m, 1H, CH), 3.02 (s, 3H, SO_2CH_3), 3.45–3.78 (m, 4H, 2 OCH_2), 4.10–4.45 (m, 4H, 2 $AcOCH_2$), 4.55 (d, 1H, O–CH–O); *IR*: 2980, 2930, 1740, 1460, 1370, 1250, 1180, 1120, 1060, 960, 840, 750 cm^{-1}; Calcd. for $C_{11}H_{22}O_7S$: C 44.28, H 7.43, S 10.75; found C 44.15, H 7.41, S 10.78.

(R)-(+)-3-Hydroxy-2-methylpropanal diethyl acetal ***9***

To a suspension of lithium aluminum hydride (5.0 g, 131 mmol) in dry tetrahydrofuran (250 ml) a solution of (*S*)-(+)-3-acetoxy-2-methanesulfonyloxymethylpropanal diethyl acetal (**8**, 6.5 g, 21.8 mmol) in tetrahydrofuran (25 ml) was added dropwise under reflux and the resulting mixture was stirred under reflux for 5 min. The reaction was then quenched by careful addition of water (30 ml) and the resulting precipitate was removed by filtration. The filtrate was concentrated by rotary evaporator and the remaining aqueous emulsion was extracted with ethyl acetate (3×30 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by vacuum-chromatography using hexane:acetone 10:1 as eluent to give 2.6 g (74%) of a colorless oil.

$[\alpha]_D$=+6.2, (c=1, acetone); *^{1}H-NMR*: 0.91 (d, 3H, CH_3), 1.24 (t, 4H, CH_3), 1.26 (t, 3H, CH_3), 2.01 (m, 1H, CH), 3.40–3.88 (m, 6H, 3 OCH_2), 4.37 (d, 1H, O–CH–O); *IR*: 3420 (br), 2980, 2930, 2880, 1460, 1370, 1350, 1120, 1060 cm^{-1}. Calcd. for $C_8H_{18}O_3$: C 59.23, H 11.18; found C 59.46, H 11.19.

(R)-(+)-3-Benzyloxy-2-methylpropanal diethyl acetal ***10***

To a solution of (*R*)-(+)-3-hydroxy-2-methylpropanal diethyl acetal (**9**, 0.81 g, 5.0 mmol) in dry tetrahydrofuran (10 ml) sodium hydride (0.4 g, 10 mmol, 60% in mineral oil) was added and the resulting mixture was heated under reflux for 1 hour. Potassium iodide (1.25 g, 7.5 mmol), tetrabutylammonium chloride (70 mg, 0.25 mmol) and benzyl chloride (0.7 ml, 6.0 mmol) were then added and heating was continued for 1 hour. After cooling, the reaction mixture was concentrated by rotary evaporator and water (3 ml) was added. The resulting emulsion was extracted with dichloromethane (3×5 ml), the combined organic extracts were dried over Na_2SO_4 and the solvent was removed to leave 1.15 g (92%) of a colorless oil.

$[\alpha]_D$=+4.2, (c=1, acetone); *^{1}H-NMR*: 1.03 (d, 3H, CH_3), 1.20 (t, 4H, CH_3), 1.21 (t, 3H, CH_3), 2.09 (m, 1H, CH), 3.30–3.82 (m, 6H, 3 OCH_2), 4.43 (d, 1H, O–CH–O), 4.50 (s, 2H, OCH_2Ph), 7.31 (m, 5H, ArH); *IR*: 2970, 2880, 1450, 1370, 1110, 1060, 1030, 740 cm^{-1}; Calcd. for $C_{15}H_{24}O_3$: C 71.39, H 9.59; found C 71.18, H 9.61.

(R)-(−)-3-Benzyloxy-2-methylpropanal ***11***

To a solution of water (2 ml), acetic acid (2 ml) and 5% hydrochloric acid (0.1 ml) (*R*)-(+)-3-benzyloxy-2-methylpropanal diethyl acetal (**10**, 0.4 g, 1.6 mmol) was added and the resulting mixture was stirred at RT for 2 hours. The reaction mixture was then extracted with ethyl acetate (2×3 ml) and the combined organic extracts were washed with saturated sodium hydrogen carbonate solution (4 ml) and brine (4 ml). After drying over Na_2SO_4 the solvent was removed by rotary evaporator. The oily residue was purified by vacuum-chromatography to yield 0.21 g (74%) of a colorless oil.

$[\alpha]_D$=−17.4, (c=1, chloroform), [(*R*)-(−)-**11**, literature: $[\alpha]_D$=−28.14, (c=1.4, chloroform); $[\alpha]_D$=−28, (c=1, chloroform)]; *^{1}H-NMR*: 1.17 (d, 3H, CH_3), 2.68 (m, 1H, CH), 3.67 (m, 2H, OCH_2), 4.53 (s, 2H, OCH_2Ph), 7.32 (m, 5H, Ar), 9.72 (d, 1H, CHO); Calcd. for $C_{11}H_{14}O_2$: C 74.13, H 7.92; found C 74.21, H 7.90.

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