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Baker's yeast mediated reduction of dihydroxyacetone derivatives

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Abstract

Several monoprotected dihydroxyacetone derivatives **4a**–**d** and their acetates **5a**–**d** were prepared and subjected to biotransformation with baker's yeast. The simple chemical modification of the substrates (i.e. transforming the relatively small hydrophilic hydroxymethyl group into a larger hydrophobic acetoxymethyl moiety) inverted the sense of enantiotope selectivity of these reductions yielding optically active diols **6a**–**d**, or their enantiomeric acetates (**7a**–**d**) and diols (*ent*-**6a**–**d**), respectively.

1. Introduction

Recently, the synthesis of optically active molecules has attracted interest due to the different effects of enantiomers. In pharmacy, these differences can be observed in therapeutic effects[1] and also in adsorption, metabolism and excretion.[2] Since biological systems are asymmetric catalysts by their nature, biocatalytic methods are widely applied for the preparation of optically active compounds.[3]

In the preparation of homochiral biologically active molecules, such as PAF (platelet-activating factor),[4] phospholipids,[5] phospholipase A_2 inhibitors,[6] and many others,[7] chiral glycerol derivatives of high enantiomeric purity might be useful C_3 building blocks. Enantiomer selective biocatalytical methods, e.g. hydrolase-catalyzed kinetic resolution of racemic glycerol derivatives such as glycerol acetonide,[8,9] or glycerol-2,3-carbonate,[10] provided moderate selectivity and 50% theoretical limit of the desired enantiomer.

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Enantiotope selective reduction of prochiral ketones theoretically enables the total conversion of the substrate into a single enantiomer of the product chiral secondary alcohol. Such prochiral ketone precursors of chiral C_3 building blocks are protected dihydroxyacetone derivatives. Accordingly, several chiral C_3 derivatives have already been prepared by chiral ruthenium complex-catalyzed asymmetric reductions.[11–13] The enantiotope selective baker's yeast reduction might be considered as a convenient biocatalytic alternative to these methods. The 3-methoxy-,[14] 3-benzoyloxy- and 3-(4-nitrobenzoyl)-oxy-[15] 1-hydroxyacetone derivatives and the 3-benzoyloxy-[15] and 3-aryloxy-[16] 1-acetoxyacetone derivatives were reduced by baker's yeast with various results. Although methods from 3-*O*-protected dihydroxyacetone derivatives leading to opposite enantiomeric forms may increase the synthetic value of the process, baker's yeast reduction of the 1-hydroxy- and 1-acetoxy-derivatives of 3-*O*-protected dihydroxyacetones with the same protective group has never been performed.

The known examples for enantiotope selective reduction of hydroxymethyl ketones or their acetates by baker's yeast[14,17–19] showed that ketones with the relatively small and hydrophilic hydroxymethyl group were reduced similarly in a geometrical sense (as a result of the sequence rules, however, the products may have different configuration labels). On the other hand, acetoxymethyl ketones were reduced with the opposite sense of enantiotopic preference. This inversion in the sense of enantiomeric preference was demonstrated by baker's yeast reduction of phenacyl alcohols and their acetates.[19–21] It should be mentioned here that reduction of hydroxymethyl ketones and their acetates by *Geotrichum* sp. 38 was reported to proceed without inversion of the sense of the enantiotopic selectivity.[22]

Since the monoprotected dihydroxyacetone derivatives are precursors of chiral C_3 building blocks, and their acetates could presumably be reduced by baker's yeast with opposite enantiopreference, we thought it worthwhile investigating the bioreduction of these compounds. Here we report the baker's yeast reduction of several synthetically useful monoprotected dihydroxyacetone derivatives **4a**–**d** and their acetates **5a**–**d**.

2. Results and discussion

The preparation of the monoprotected dihydroxyacetone derivatives **4a**–**d** and their acetates **5a**–**d** was straightforward starting from dihydroxyacetone **1** as outlined in Fig. 1. Ketones **4a**[15] and **4b** were prepared by monoacylation of the dihydroxyacetone (**1**, existing mostly in dimeric form) by benzoyl chloride and pivaloyl chloride, respectively. The benzyloxymethyl ketone **4c** was obtained[11] from the dimethyl ketal of dihydroxyacetone **2** by subsequent benzylation and acidic deketalization. Monosilylation[23] of dihydroxyacetone **1** provided the ketone **4d** smoothly. The acetoxymethyl ketones **5a**–**d** were obtained from their hydroxymethyl precursors (**4a**–**d**, respectively) by simple acetylation.

Since stereoselectivity of baker's yeast-catalyzed reactions may depend considerably on the reaction conditions (pH, solvent, additives, etc.), it was desirable to find the optimum. Hence, reaction conditions of the baker's yeast reduction of 1-benzoyloxy-3-hydroxypropan-2-one **4a** were investigated (Table 1).

The different reaction conditions were chosen by analogies with published modifications of reaction conditions increasing the stereoselectivity of carbonyl-reductions by baker's yeast. Reductions in apolar hydrocarbons with 'non-fermenting' baker's yeast resulted in increased selectivities.[24,25] Such selectivity enhancement was obtained by using N_2-atmosphere and cosolvent like DMSO.[15] Some sulfur-containing additives, such as L-cysteine or cysteamine, also produced significant selectivity enhancement in the reductions of 1-acetoxyalkan-2-ones.[26] It should be noted, however, that these additives were also used to suppress the hydrolysis of the ester function in these reactions. Ethanolamine as a possible substitute for the L-cysteine or cysteamine was also tested as an additive.

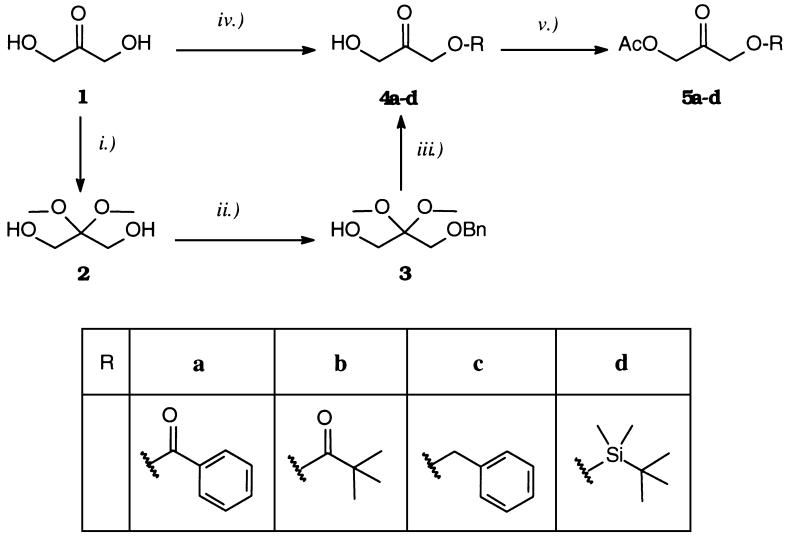


Figure 1. Preparation of hydroxymethyl ketones **4a**–**d** and their acetates **5a**–**d**. *Reagents and solvents*: (i) trimethyl orthoformate in MeOH; (ii) BnBr, NaH in THF; (iii) 3 M HCl; (iv) BzCl, cat. DMAP, pyridine (for **4a**), PivCl, cat. DMAP, pyridine (for **4b**) or TBDMSCl, imidazole in THF (for **4d**); (v) Ac_2O, cat. DMAP, Et_3N in ethyl acetate (for **5a**,**c**,**d**) or AcCl, cat. DMAP, Et_3N in THF (for **5b**)

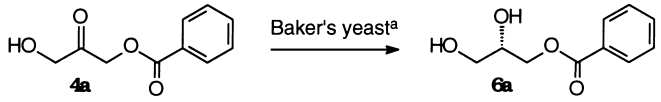
Although alcohol dehydrogenases can operate in ethanol as solvent, no reduction was observed in neat ethanol (Entry 1). Reactions with the traditional 'non-fermenting' yeast (Entry 2) or with 'non-fermenting' yeast in the presence of ethanol as coupled substrate in cofactor regeneration under N_2 (Entry 3) proceeded with moderate selectivities. The low isolated yields in hexane (Entries 4, 5 and 8) indicated low productivity/conversion without significant increase in selectivity. The productivities and selectivities of systems containing glucose were better (Entries 6–9). The best selectivity yielding homochiral diol **6a** was achieved by 'fermenting' baker's yeast under anerobic conditions with ethanol as cosolvent and L-cysteine as an additive (Entry 9).

The reaction conditions for the further compounds were optimized in a similar way. The reductions of these ketones **4b**–**d** and **5a**–**d** were conducted under the conditions which gave the highest enantiotopic selectivities, as listed in Table 2. The results achieved by the baker's yeast reduction of the hydroxymethyl ketones **4a**–**d** and their acetates **5a**–**d** confirmed the previous findings[19–21] and our expectations: the geometrical sense of the enantiotopic preference altered in all the cases when the hydroxymethyl ketones **4a**–**d** versus their acetates **5a**–**d** were reduced.

In the case of reduction of acetates **5a**–**d**, however, substantial amounts of diols *ent*-**6a**–**d** were also produced. Configuration of these diols *ent*-**6a**–**d** was opposite to the diols **6a**–**d** from reduction of the hydroxymethyl ketones **4a**–**d**. These data confirmed that diols *ent*-**6a**–**d** were produced mostly by reduction of the acetoxymethyl ketones **5a**–**d** followed by an enzymatic hydrolysis, and were consistent with our previous results on baker's yeast reduction of 1-acetoxy-3-aryloxypropan-2-ones,[16] where the geometrical sense of enantiotopic preference was the same as for the present ketones **5a**–**d** and different amounts of hydrolyzed products from enzymatic hydrolysis were also obtained.[27]

Since the hydroxymethyl ketones **4a**–**d** were reduced substantially slower and with opposite enantiotopic preferences than the acetoxymethyl ketones **5a**–**d**, our results further support the hypothesis[19–21] assuming that these two classes of ketones are reduced mostly by different enzymes of the baker's yeast system.

Table 1
Dependence of the stereoselectivity on the reaction conditions in reduction of ketone **4a**



Entry	Yeast (g)	Buffer (Atm.) (ml)	Solvent (ml)	Additive(s) (g)	Time (h)	Y [b] (%)	E.e. [c] (%)
1	12	-	EtOH (100)	-		no reaction	
2	12	60	-	-	24	60	56
3	8	60 (N_2)	EtOH (6)	-	20	56	64
4	15	15	hexane (150), EtOH (1.5), DMSO (1.5)	-	24	46	77
5	15	15	hexane (150), EtOH (3)	-	22	36	85
6	8	60 (N_2)[d]	EtOH (0.6), DMSO (0.6)	glucose (6)	4	56	85
7	8	60 (N_2)[d]	EtOH (1.2)	glucose (6), ethanolamine (0.12)	4	76	86
8	15	15	hexane (150), DMSO (1.5)	glucose (6)	24	42	89
9	**8**	**60 (N_2)[d]**	**EtOH (1.2)**	**glucose (6) L-cysteine (0.3)**	**20**	**80**	**>97**

[a] Standard conditions: 500 mg of **4a**, 0.15 M pH= 7.0 phosphate buffer, baker's yeast from Budafok factory; [b] Yields refer to products purified by preparative column chromatography; [c] Absolute configuration was taken from Ref. 15; enantiomeric excess was determined from the ^{1}H-NMR spectrum of the (*R*)-MTPA ester of **7a**; [d] Substrate was added 30 minutes after starting the fermentation.

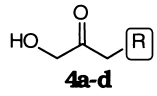
3. Conclusions

Our results showed that the monoprotected dihydroxyacetone derivatives **4a–d** and their acetates **5a–d** are synthetically useful precursors of different chiral C_3 building blocks. In accordance with the previous findings, these hydroxymethyl **4a–d** and acetoxymethyl **5a–d** ketones were reduced by baker's yeast oppositely in a geometrical sense, yielding optically active diols **6a–d**, or monoacetates **7a–d** and the enantiomeric diols *ent*-**6a–d**, respectively.

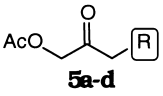
4. Experimental

The ^{1}H NMR spectra were recorded on a Bruker AW-250 spectrometer operating at 250 MHz. For enantiomeric excess determinations, a Bruker DRX-500 spectrometer operating at 500 MHz was used. All spectra were taken in $CDCl_3$ solution and chemical shifts are expressed in ppm values from TMS as internal standard on 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 (using hexane:acetone, 10:4, if not stated

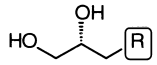
Table 2
Results for baker's yeast reduction of monoprotected dihydroxyacetone derivatives **4a–d** and their acetates **5a–d**



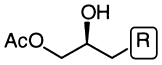
4a-d



5a-d

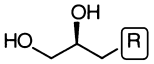


6a-d



7a-d

+



ent-**6a-d**

R	Method [a]	Yield %	Conf.	E.e. %	Method [a]	Yield %	Conf. [b]	E.e. %	Yield %	Conf.	E.e. %
a	**A**	80	*S*	> 97	**D**	54	*R*[b]	68	22	*R*	19
b	**B**	71	*S*	72	**E**	56	*R*[b]	>95	9	*R*	46
c	**A**	50	*S*	55	**F**	60	*S*[b]	85	20	*R*	33
d	**C**	21	*S*	59	**F**	21	*R*[b]	> 97	25	*R*	77

[a] *Common conditions*: 500 mg of ketone (**4a-d, 5a-d**), in 0.15 M pH=7 phosphate buffer, baker's yeast from Budafok factory. *Methods*: **A**, 20 h reaction with yeast (8 g) in buffer (60 ml) under N_2 containing 2% ethanol, glucose (6 g) and L-cysteine (1 eq.); **B**, 24 h reaction with yeast (12 g) in buffer (100 ml) under N_2 containing 2% ethanol and glucose (5 g); **C**, 48 h reaction with yeast (12 g) in buffer (100 ml) under N_2 containing 2% ethanol and glucose (5 g); **D**, 3 h reaction with yeast (8 g) in buffer (60 ml) under N_2 containing 2% ethanol, 2% DMSO and glucose (6 g); **E**, 1.5 h reaction with yeast (12 g) in buffer (100 ml) containing 5% ethanol and glucose (5 g); **F**, 4 h reaction with yeast (8 g) in buffer (60 ml) under N_2 containing 2% ethanol, 2% DMSO and glucose (6 g); [b] Due to a change in group preferences, the absolute configuration *S* in the case of the benzyloxy product **7c** means the same *sense* of stereochemistry as in the case of the other acetates **7a,b,d**. For determination of the configurations, see Experimental section.

otherwise). Spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution and heating of the dried plates. Preparative chromatographic separations were performed using vacuum-chromatography[28] on a Merck Kieselgel 60 (0.063–0.200 mm). Chemicals were products of Fluka or Aldrich. All solvents used were freshly distilled. Baker's yeast manufactured by Budafok factory, Budapest, was obtained from a local store.

*4.1. 1-Benzoyloxy-3-hydroxypropan-2-one **4a**[15]*

The reaction[15] starting from 1,3-dihydroxyacetone (**1**, 20 g, 222 mmol) yielded the desired ketone (**4a**, 14 g, 32%) as a colorless crystalline solid. Mp: 92–93°C (lit.:[15] 95–97°C); IR (KBr): 3430 (br), 1718, 1602, 1452, 1376, 1278, 1180, 1111, 1072, 924, 811, 709 cm^{-1}; ^1H NMR: 4.50 (s, 2H, O-CH_2), 5.03

(s, 2H, CH_2-OBz), 5.53 (br s, 1H, OH), 7.47 (t, 2H, *m*-ArH), 7.58 (t, 1H, *p*-ArH), 8.10 (d, 2H, *o*-ArH). Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.66; H, 5.21.

*4.2. 1-Hydroxy-3-pivaloyloxypropan-2-one **4b***

To a stirred solution of 1,3-dihydroxyacetone (**1**, 6.75 g, 75 mmol) and 4-(dimethylamino)pyridine (0.1 g) in pyridine (45 ml) pivaloyl chloride (6.1 ml, 50 mmol) was added dropwise at 24–25°C. After stirring the resulting mixture at room temperature overnight pyridine was evaporated in vacuo. The residue was diluted with ethyl acetate (100 ml) and washed with 5% HCl (2×20 ml). The aqueous phase was re-extracted with ethyl acetate (2×30 ml). The combined organic phases were washed with saturated $NaHCO_3$ solution (30 ml) and brine (30 ml). After drying over $MgSO_4$ the solvent was evaporated and the residual solid was recrystallized from hexane to yield a crystalline product (**4b**, 3.75 g, 43%). IR (KBr): 3408, 2960, 2930, 1735, 1725, 1470, 1360, 1280, 1170, 1070, 880 cm^{-1}; ^1H NMR: 1.25 (s, 9H, 3 CH_3), 4.37 (s, 2H, O-CH_2), 4.73 (s, 2H, CH_2-OPiv). Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.40; H, 8.07.

*4.3. 1-Benzyloxy-3-hydroxypropan-2-one **4c**[11]*

Preparation of the monobenzylated dihydroxyacetone **4a**[11] started from 1,3-dihydroxyacetone (**1**, 2.25 g, 25 mmol) and via the intermediates 2,2-dimethoxypropane-1,3-diol [**2**, 90%, ^1H NMR: 3.31 (s, 6H, 2 OCH_3), 3.67 (s, 4H, 2 CH_2O] and 1-benzyloxy-2,2-dimethoxypropan-3-ol [**3**, 52%, ^1H NMR: 3.27 (s, 6H, 2 OCH_3), 3.53 (s, 2H, CH_2-OBn), 3.70 (s, 2H, O-CH_2), 4.58 (s, 2H, OCH_2Ph), 7.32 (m, 5H, ArH)] resulted in a homogeneous oily product (**4c**, 1.74 g, 39% overall). IR: 3440 (br), 2869, 1731, 1496, 1434, 1209, 1103, 1028, 741 cm^{-1}; ^1H NMR: 4.19 (s, 2H, CH_2-OBn), 4.47 (s, 2H, O-CH_2), 4.60 (s, 2H, OCH_2Ph), 7.35 (m, 5H, ArH). Calcd for $C_{10}H_{10}O_4$: C, 66.65; H, 6.71. Found: C, 66.33; H, 6.73.

*4.4. 1-(*tert*-Butyldimethylsilyl)oxy-3-hydroxypropan-2-one **4d**[23]*

Silylation[23] from 1,3-dihydroxyacetone (**1**, 2.0 g, 22.2 mmol) provided the desired ketone (**4d**, 1.39 g, 60%) as a colorless oil. IR: 3430 (br), 2970, 2940, 2890, 2870, 1740, 1490, 1270, 1105, 855, 795 cm^{-1}; ^1H NMR: 0.03 (s, 6H, 2 CH_3-Si), 0.91 (s, 9H, 3 CH_3), 4.30 (s, 2H, CH_2-OTBDMS), 4.49 (s, 2H, O-CH_2). Calcd for $C_9H_{20}O_3Si$: C, 52.90; H, 9.87. Found: C; 52.73; H, 9.88.

*4.5. Acetylation of hydroxymethyl ketones **4a–d***

Method A (for **4a, 4c** and **4d**): To a stirred solution of hydroxymethyl ketone (**4a**, 7 g, 36 mmol), triethylamine (7 ml, 50 mmol) and 4-(dimethylamino)pyridine (0.1 g) in ethyl acetate (70 ml) acetic anhydride (4 ml, 42 mmol) was added dropwise at room temperature and the resulting mixture was stirred for 90 min. The reaction mixture was washed with 10% HCl (2×140 ml), 1 M Na_2CO_3 (140 ml) and dried over Na_2SO_4. Evaporation of the solvent resulted in an oil. The same procedure was used for ketones **4c** (1.1 g, 6 mmol) and **4d** (1.70 g, 8.32 mmol).

Method B (for **4b**): To a stirred solution of 1-hydroxy-3-pivaloyloxypropan-2-one (**4a**, 2 g, 11.5 mmol), triethylamine (1.75 g, 13.8 mmol) and 4-(dimethylamino)pyridine (50 mg) in THF (25 ml) acetyl chloride (1.08 g, 13.8 mmol) was added dropwise and the mixture was stirred for 90 min. Ethyl acetate (100 ml) and 5% HCl solution (15 ml) were added to the mixture and the forming layers were separated. The aqueous layer was extracted with ethyl acetate (50 ml). The combined organic phases were washed with

saturated $NaHCO_3$ solution (25 ml), saturated Na_2CO_3 solution and dried over Na_2SO_4. After removal of the solvent, preparative vacuum column chromatography of the residue yielded an oil **5b**.

*4.6. 1-Acetoxy-3-benzoyloxypropan-2-one **5a***

Yield: 6.3 g, 75%. IR: 3069, 2991, 2939, 1737, 1729, 1601, 1451, 1417, 1372, 1277, 1228, 1177, 1101, 1052, 1025, 977, 834, 715 cm^{-1}; ^1H NMR: 2.20 (s, 3H, CH_3-CO), 4.86 (s, 2H, CH_2-OAc), 5.01 (s, 2H, CH_2-OBz), 7.46 (t, 2H, *m*-ArH), 7.58 (t, 1H, *p*-ArH), 8.09 (d, 2H, *o*-ArH). Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12; Found: C, 61.21; H, 5.10.

*4.7. 1-Acetoxy-3-pivaloyloxypropan-2-one **5b***

Yield: 1.9 g, 77%. IR: 2970, 1735, 1730, 1725, 1470, 1360, 1470, 1360, 1280, 1215, 1150, 1130, 1055 cm^{-1}; ^1H NMR: 1.22 (s, 9H, 3 CH_3), 2.12 (s, 3H, CH_3-CO), 4.69 (s, 2H, O-CH_2), 4.70 (s, 2H, O-CH_2). Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46; Found: C, 55.45; H, 7.48.

*4.8. 1-Acetoxy-3-benzyloxypropan-2-one **5c***

Yield: 1.23 g, 92%. IR: 3032, 2937, 2860, 1739, 1732, 1455, 1410, 1374, 1235, 1104, 1071, 1027, 742, 700 cm^{-1}; ^1H NMR: 2.21 (s, 3H, CH_3-CO), 4.19 (s, 2H, CH_2-OBn), 4.63 (s, 2H, OCH_2Ph), 4.94 (s, 2H, CH_2-OAc), 7.38 (m, 5H, ArH). Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35; Found: C, 65.00; H, 6.33.

*4.9. 1-Acetoxy-3-(*tert*-butyldimethylsilyl)oxypropan-2-one **5d***

Yield: 1.90 g, 93%. IR: 2965, 2940, 2895, 2870, 1755, 1740, 1490, 1420, 1390, 1270, 1250, 1110, 1090, 855, 795 cm^{-1}; ^1H NMR: 0.03 (s, 6H, 2 CH_3-Si), 0.87 (s, 9H, 3 CH_3), 2.08 (s, 3H, CH_3-CO), 4.19 (s, 2H, CH_2-OTBDMS), 4.87 (s, 2H, CH_2-OAc). Calcd for $C_{11}H_{22}O_4Si$: C, 53.63; H, 9.00; Found: C, 53.81; H, 9.02.

*4.10. Baker's yeast-catalyzed stereoselective reduction of ketones **4a–d**, **5a–d***

4.10.1. General method

Yeast was added to the media as indicated in Table 2. After stirring the resulting cell suspension for 30 min, the corresponding ketone (**4a–d**, **5a–d**; 500 mg) was added. When indicated, the substrate was previously dissolved in ethanol (2–4 ml). The reaction mixture was stirred (time given in Table 2). The resulting mixture was extracted with ethyl acetate (2×150 ml), the combined ethyl acetate layers were washed with brine, dried over $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by preparative vacuum column chromatography (hexane:acetone, 10:1) to give oily product(s) in yields indicated in Table 2.

*4.10.2. 1-Benzoyloxypropane-2,3-diol **6a***

IR: 3400 (br), 2952, 1714, 1602, 1452, 1379, 1316, 1278, 1178, 1117, 1071, 1027, 712 cm^{-1}; ^1H NMR: 3.50–3.80 (m, 2H, O-CH_2), 4.12 (m, 1H, O-CH), 4.37 (m, 2H, CH_2-OBz), 7.43 (t, 2H, *m*-ArH), 7.54 (t, 1H, *p*-ArH), 8.02 (d, 2H, *o*-ArH).

4.10.3. 1-Pivaloyloxypropane-2,3-diol ***6b***

IR: 3450, 2980, 2960, 1730, 1480, 1460, 1370, 1280, 1170, 1045 cm^{-1}; ^1H NMR: 1.22 (s, 9H, 3 CH_3), 3.59 and 3.69 (2 dd, 2H, O-CH_2), 3.94 (m, 1H, O-CH), 4.16 (m, 2H, CH_2-OPiv).

4.10.4. 1-Benzyloxypropane-2,3-diol ***6c***

IR: 3385 (br), 2924, 2867, 1646, 1496, 1453, 1364, 1207, 1074, 925, 865, 738, 698 cm^{-1}; ^1H NMR: 3.50–3.78 (m, 4H, O-CH_2), 3.87 (m, 1H, O-CH), 4.55 (s, 2H, OCH_2Ph), 7.35 (m, 5H, ArH).

*4.10.5. 1-(*tert-*Butyldimethylsilyl)oxypropane-2,3-diol* ***6d***

IR: 3400, 2970, 2945, 2895, 2865, 1485, 1275, 1250, 1130, 1090, 850, 795 cm^{-1}; ^1H NMR: 0.03 (s, 3H, CH_3-Si), 0.06 (s, 3H, CH_3-Si), 0.88 (s, 9H, 3 CH_3), 3.55–3.75 (m, 5H, 2 O-CH_2 and O-CH).

4.10.6. 1-Acetoxy-3-benzoyloxypropan-2-ol ***7a***

IR: 3462 (br), 3065, 2958, 1727, 1721, 1606, 1452, 1375, 1316, 1276, 1178, 1116, 1071, 1047, 1027, 713 cm^{-1}; ^1H NMR: 2.11 (s, 3H, CH_3-CO), 4.25 (m, 3H, CH_2-OAc and O-CH), 4.42 (m, 2H, CH_2-OBz), 7.44 (t, 2H, *m*-ArH), 7.58 (t, 1H, *p*-ArH), 8.03 (d, 2H, *o*-ArH).

4.10.7. 1-Acetoxy-3-pivaloyloxypropan-2-ol ***7b***

IR: 3400 (br), 2980, 2960, 1730, 1725, 1475, 1450, 1370, 1280, 1170, 1045 cm^{-1}; ^1H NMR: 1.23 (s, 9H, 3 CH_3), 2.09 (s, 3H, CH_3-CO), 4.05–4.25 (m, 5H, 2 O-CH_2 and O-CH).

4.10.8. 1-Acetoxy-3-benzyloxypropan-2-ol ***7c***

IR: 3445, 3063, 3030, 1738, 1496, 1454, 1369, 1244, 1098, 1045, 740, 699 cm^{-1}; ^1H NMR: 2.08 (s, 3H, CH_3-CO), 3.52 (m, 2H, CH_2OBn), 4.05 (m, 1H, O-CH), 4.16 (m, 2H, CH_2OAc), 4.56 (s, 2H, OCH_2Ph), 7.33 (m, 5H, ArH).

*4.10.9. 1-Acetoxy-3-(*tert-*butyldimethylsilyl)oxypropan-2-ol* ***7d***

IR: 3460, 2960, 2935, 2895, 2860, 1755, 1735, 1480, 1405, 1380, 1270, 1250, 1120, 1050, 850, 795 cm^{-1}; ^1H NMR: 0.02 (s, 3H, CH_3-Si), 0.05 (s, 3H, CH_3-Si), 0.86 (s, 9H, 3 CH_3), 2.04 (s, 3H, CH_3-CO), 3.58 (m, 2H, CH_2-OTBDMS), 3.76–4.01 (m, 2H, CH_2-OAc), 4.09 (m, 1H, O-CH).

*4.11. Determination of enantiomeric excess and absolute configuration of the diols (****6a–d****,* ent-***6a–d****) and monoacetates* ***7a–d***

4.11.1. Enantiomeric excess determination

4.11.1.1. (A) MTPA derivatization of the optically active monoacetates ***7a–d****.* A sample of each monoacetate (**7a**–**d**, 50 μmol, ca.12 mg) with measured optical rotation was converted into its (*R*)-MTPA ester [350 μl of 5% (*R*)-MTPA-Cl solution in carbon tetrachloride, pyridine (25 μl), DMAP (2 mg), 50°C, 3 h]. A similar reaction was carried out with the racemic monoacetates *rac*-**7a**–**d**. The diastereomer ratio referring to the enantiomeric excess of the monoacetates **7a**–**d** was determined from the ^1H NMR spectra of the MTPA ethers [500 MHz, CH_3CO signals: (*R,R*)-**7a**-MTPA: 2.07 ppm, (*R,S*)-**7a**-MTPA: 2.01 ppm, (*R,R*)-**7b**-MTPA: 2.08 ppm, (*R,S*)-**7b**-MTPA: 2.02 ppm, (*R,S*)-**7c**-MTPA: 2.03 ppm, (*R,R*)-**7c**-MTPA: 1.97 ppm, (*R,R*)-**7d**-MTPA: 2.05 ppm, (*R,S*)-**7d**-MTPA: 1.98 ppm].

4.11.1.2. (B) Preparation of diacetates ***8a–d*** *from monoacetates* ***7a–d*** *and diols* ***6a–d*** *or* ent-***6a–d****.* Another aliquot of each sample **7a**–**d** used in the MTPA ee determination was acetylated [**7a**–**d**: 0.1 g,

Et_3N (1.4 mmol), DMAP (10 mg), Ac_2O (1.1 mmol) in EtOAc (1 ml), at rt, 90 min; purified yields over 90%] to give the corresponding oily diacetate **8a–d** with known enantiomeric excess value.

Diacetates **8a–d** or *ent*-**8a–d** were also prepared from the optically active diols [**6a–d** or *ent*-**6a–d**: 0.1 g, Et_3N (2.8 mmol), DMAP (15 mg), Ac_2O (2.2 mmol) in EtOAc (1 ml), at rt, 90 min; purified yields over 90%] as well. Optical rotations of these diacetates **8a–d** or *ent*-**8a–d** compared to the rotation data of the diacetates **8a–d** with known enantiomeric purities refer to the enantiomeric composition of the corresponding parent diol **6a–d** or *ent*-**6a–d**.

*4.11.2. 1-Benzoyloxy-2,3-diacetoxypropane **8a***

IR: 3065, 2962, 1753, 1747, 1735, 1602, 1452, 1372, 1316, 1260, 1224, 1178, 1115, 1071, 1051, 1026, 713 cm^{-1}; ^1H NMR: 2.11 (s, 3H, CH_3-CO), 2.13 (s, 3H, CH_3-CO), 4.20–4.65 (m, 4H, 2 O-CH_2), 5.43 (m, 1H, CH-OAc), 7.45 (t, 2H, *m*-ArH), 7.58 (t, 1H, *p*-ArH), 8.04 (d, 2H, *o*-ArH).

*4.11.3. 2,3-Diacetoxy-1-pivaloyloxypropane **8b***

IR: 2970, 1745, 1735, 1725, 1470, 1360, 1280, 1220, 1145, 1040 cm^{-1}; ^1H NMR: 1.20 (s, 9H, 3 CH_3), 2.06 (s, 3H, CH_3-CO), 2.08 (s, 3H, CH_3-CO), 4.12–4.35 (m, 4H, 2 O-CH_2), 5.28 (m, 1H, CH-OAc).

*4.11.4. 1-Benzyloxy-2,3-diacetoxypropane **8c***

IR: 3010, 2925, 2835, 1744, 1727, 1496, 1450, 1365, 1240, 1100, 1030, 950, 735, 695 cm^{-1}; ^1H NMR: 2.00 (s, 3H, CH_3-CO), 2.04 (s, 3H, CH_3-CO), 3.56 (m, 2H, CH_2-OBn), 4.23 (m, 2H, CH_2-OAc), 4.50 (s, 2H, OCH_2Ph), 5.18 (m, 1H, CH-OAc), 7.29 (m, 5H, ArH).

*4.12. 1-(*tert*-Butyldimethylsilyl)oxy-2,3-diacetoxypropane **8d***

IR: 2965, 2940, 2895, 2870, 1755, 1485, 1385, 1270, 1245, 1130, 1060, 850, 795 cm^{-1}; ^1H NMR: 0.03 (s, 3H, CH_3-Si), 0.06 (s, 3H, CH_3-Si), 0.88 (s, 9H, 3 CH_3), 2.05 (s, 3H, CH_3-CO), 3.69 (m, 2H, CH_2-OTBDMS), 4.09–4.33 (m, 2H, CH_2-OAc), 5.05 (m, 1H, CH-OAc).

*4.13. Determination of the absolute configuration of the monoacetates **7a–d** and diols **6a–d** and* ent-*6a–d***

Since the absolute configuration of a benzoyloxy **6a**,[15] and the benzyloxy compounds **6c**[11,29] and **7c**[30,31] are known, the diacetates **8a**,**c** prepared either from the monoacetates **7a**,**c** or the diols **6a**,**c** and *ent*-**6a**,**c** were suitable for determination of the absolute configuration of these compounds.

For determination of the absolute configuration of pivaloyloxy compounds **7b**, **6b**, and *ent*-**6b**, an optically active sample of (*R*)-3-acetoxypropane-1,2-diol {$[\alpha]_D$=−9.9 (*c* 2, pyridine) [lit.:[32] $[\alpha]_D$=−9.2, (*c* 1.7, pyridine)] obtained by catalytic hydrogenation from (*R*)-3-acetoxy-1-benzyloxypropan-2-ol manufactured by PfL catalysis[30]} was converted to (*S*)-3-acetoxy-1-pivaloyloxypropane-2-ol *ent*-**7b** proving the absolute configuration of **7b**. Configurations of the diols **6b** and *ent*-**6b** were determined via their diacetates **8b** and *ent*-**8b** compared to the diacetate **8b** from the monoacetate **7b**.

The optical rotation of (*R*)-1-(*tert*-butyldimethylsilyl)oxypropane-2,3-diol **6d** was reported[33] as $[\alpha]_D$=−0.6 (*c* 1.31, $CHCl_3$). Since the small specific rotation values of the polar 1,2-diols are often unreliable,[34] absolute configuration of the diols **6d** and *ent*-**6d** was determined by an independent method. Silylation of the above (*R*)-3-acetoxypropane-1,2-diol with TBDMS-Cl (imidazole/THF) gave (*S*)-1-acetoxy-3-(*tert*-butyldimethylsilyl)oxypropan-2-ol {*ent*-**7d**, $[\alpha]_D$=−14.1 (*c* 1, MeOH)}. The yeast

reduction resulted, however, in (*R*)-monoacetate {**7d**, $[\alpha]_D$=+17.6 (*c* 1, MeOH)}. Acylation of this (*R*)-monoacetate **7d** resulted in (*R*)-diacetate {(*R*)-**8d**, $[\alpha]_D$=+19.8 (*c* 1, MeOH)}. Since a diol fraction {*ent*-**6d**, $[\alpha]_D$=+0.9 (*c* 1, $CHCl_3$); $[\alpha]_D$=+9.2, (*c* 1, methanol)} from another reduction of the acetoxymethyl ketone **5d** also resulted in (*R*)-diacetate {(*R*)-**8d**, $[\alpha]_D$=+19.1 (*c* 1, MeOH)}, this diol *ent*-**6d** should have the (*R*)-configuration. Therefore, the above cited specific rotation data for the (*R*)-1-(*tert*-butyldimethylsilyl)oxypropane-2,3-diol should be revised.

The absolute configurations, enantiomeric excesses and optical rotation values of diols **6a**–**d** and monoacetates **7a**–**c** prepared by baker's yeast reduction and their diacetate derivatives **8a**–**d** are given in Table 3.

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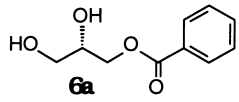
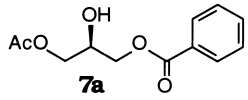
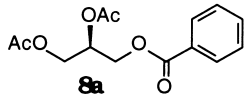
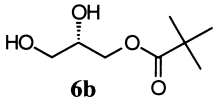
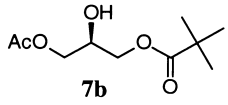
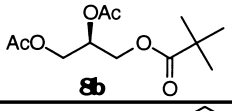
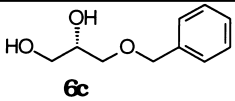
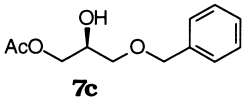
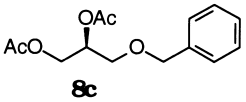
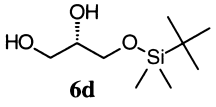
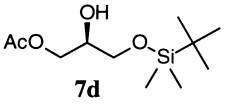
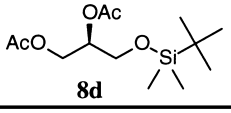
Table 3
Enantiomeric excess, specific rotations and absolute configurations for compounds **6a–d**, **7a–d** and **8a–d**

Compound	Config.	Source	$[\alpha]_D$ (c, solvent)	E.e. %	Method
 **6a**	*S*	Ref. 15	+13.7 (2, pyridine)	> 97	from **8a**
 **7a**	*R*	from **8a**	not determined	68	from its MTPA ester
 **8a**	*R*	from **6a**	+6.8 (1, ethanol)	68	from **7a**
 **6b**	*S*	from **8b,**	+6.3 (1, ethanol)	72	from **8b**
 **7b**	*R*	compared to *ent*-**7b**, see text	+5.7 (1, ethanol)	>95	from its MTPA ester
 **8b**	*R*	from **7b**	+0.87 (1, ethanol)	46	from **7b**
 **6c**	*S*	Ref. 29	-3.2 (10, benzene)	55	from **8c**
 **7c**	*S*	Ref. 30	+3.4 (1, $CHCl_3$)	85	from its MTPA ester
 **8c**	*S*	from **7c**	+15.2 (1, ethanol)	85	from **7c**
 **6d**	*S*	from **8d**, see text	-5.8 (1, methanol)	59	from **8d**
 **7d**	*R*	compared to *ent*-**7d**, see text	+17.6 (1, methanol)	>97	from its MTPA ester
 **8d**	*R*	from **7d**	+15.6 (1, methanol)	77	from **7d**

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