# Microbial Resolution and Asymmetric Reduction related to Optically Active 1,3-Diphenylpropane-1,3-diol

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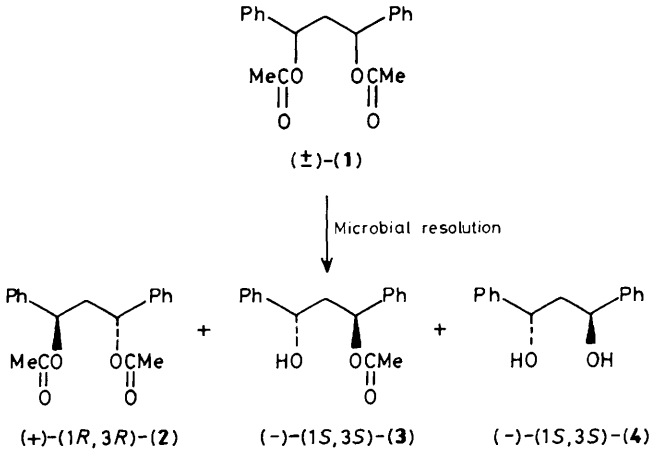
An efficient microbial resolution of 1,3-diphenylpropane-1,3-diol (**4**) has been achieved by exposing the corresponding diacetate to *Trichoderma viride*; a reductive cleavage of chiral acetals (**6**) derived from (**4**) with hydride reagent ($Br_2AlH$, $Cl_2AlH$) affords optically active alcohols (**8**) of high enantiomeric purities.

While investigating novel asymmetric cleavage[1] of chiral acetals, we found that 1,3-diphenylpropane-1,3-diol (**4**) is an excellent chiral inducing source in reductive cleavage of chiral acetals. In this communication we report on efficient microbial stereodifferentiating hydrolysis of the diester (**1**) to provide the optically active 1,3-diol (**4**), and an asymmetric cleavage of chiral acetals (**6**) utilizing (**4**) as the chiral inducing source.

Incubation of (±)-diester (**1**)† (1 g) with the resting cell of *Trichoderma viride* (IFO 9065) (*T. koningii*)[3] at 25 °C for 14 h gave a 49 : 10 : 41 mixture of the recovered diester (**2**), the monoester (**3**), and the diol (**4**) which was chromatographed to yield (+)-(1*R*,3*R*)-(**2**)‡ (470 mg), $[\alpha]_D^{26}$ +66.1° (MeOH) [85% enantiomeric excess (e.e.)].§ (−)-(1*S*,3*S*)-(**3**) (58 mg), $[\alpha]_D^{26}$ −6.6° (MeOH) (15% e.e.), and (−)-(1*S*,3*S*)-(**4**)¶ (270 mg), m.p. 160—161 °C, $[\alpha]_D^{26}$ −72.0° (MeOH) (100% e.e.),** respectively.




† The racemic substrate (**1**) was readily prepared from the corresponding diol.[2] All new compounds gave satisfactory spectra and elemental analytical data.

‡ C.d. spectral comparison with (−)-(*S*)-1-phenylethyl acetate[4] indicated a (1*R*,3*R*)-configuration for (+)-(**2**).

§ The optical purity of (+)-(**2**) was determined by h.p.l.c. analysis with a column packed with (+)-poly(triphenylmethyl methacrylate) (elution with methanol).[5]

¶ *T. viride* catalysed hydrolysis of (±)-(**1**) (1 g) at 25 °C for 24 h gave a 40 : 6 : 54 mixture of (**2**), (**3**), and (**4**) which was chromatographed to afford (+)-(1*R*,3*R*)-(**2**) (270 mg) (100% e.e.), (+)-(1*R*,3*R*)-(**3**) (35 mg) (86% e.e.), and (−)-(1*S*,3*S*)-(**4**) (460 mg) (81% e.e.). Pig liver esterase[6] catalysed hydrolysis of (±)-(**1**) (1 g) at pH 8.0 for 7 days gave a 48 : 8 : 44 mixture of (**2**), (**3**), and (**4**) which was chromatographed to give (−)-(1*S*,3*S*)-(**2**) (430 mg) (84% e.e.), (−)-(1*S*,3*S*)-(**3**) (50 mg) (8% e.e.), and (+)-(1*R*,3*R*)-(**4**) (300 mg) (92% e.e.).

** The absolute configurations and optical purities of (−)-(**3**) and (−)-(**4**), were determined by acetylation back to the (−)-diester (**2**).

Following Yamamoto and co-workers' procedure,[1] an ethereal solution of the aluminium hydride reagent ($Cl_2AlH$, $Br_2AlH$) was prepared *in situ* from $LiAlH_4$ and $AlX_3$ (X = Cl, Br), and then cooled (Table 1). The acetal (**6**) (1 equiv.) derived from (−)-(1*S*,3*S*)-(**4**) and the carbonyl compound (**5**), was added to this hydride reagent (3 equiv.). After stirring at this temperature for a few hours, the reaction mixture was quenched with 2 M HCl and the product was extracted with diethyl ether. Chromatography on silica provided the alcohol (**7**) in high yield. Removal of the chiral auxiliary in (**7**) was carried out using one of two methods: (i) reductive cleavage of (**7**) with sodium in liquid ammonia (for $R^1$ = Me, $R^2$ =

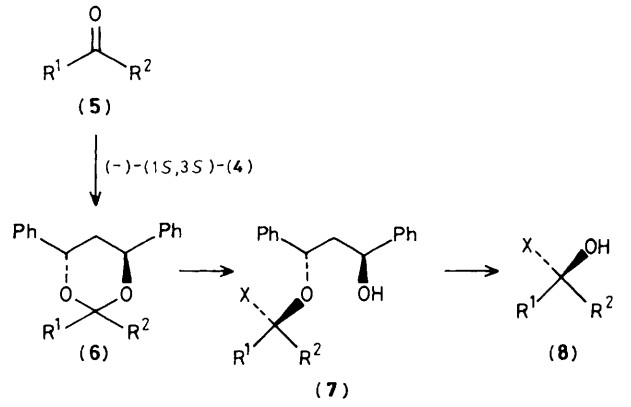
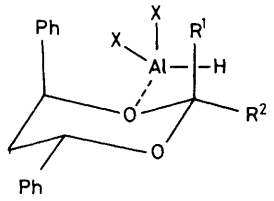



**Table 1.** Reduction of chiral acetals (**6**) with hydride reagents.[a]

| Acetal (**6**)[b] $R^1$ | $R^2$ | Hydride reagent | Conditions °C | h | Alcohol (**8**) X | Yield % | % e.e. (configuration) |
|---|---|---|---|---|---|---|---|
| Me | n-$C_6H_{13}$ | $Cl_2AlH$ | 0 | 2 | H | 88 | 81[c](*S*) |
| | | $Br_2AlH$ | 0 | 2 | H | 86 | 96[c](*S*)[e] |
| Me | Ph | $Cl_2AlH$ | 0 | 2 | H | 87 | 98[d](*S*) |
| | | $Br_2AlH$ | 0 | 2 | H | 84 | 99[d](*S*)[e] |
| H | Ph | $Br_2AlD$[f] | 0 | 2 | D | 88 | 58[g](*R*) |
| | | $Br_2AlD$[f] | −15 | 3 | D | 85 | 70[g](*R*)[e] |

[a] Reduction of (**6**) was carried out as described in text. [b] Prepared from (**5**) with (+)-(1*S*,3*S*)-1,3-diphenylpropane-1,3-diol (**4**) in the presence of a catalytic amount of pyridinium toluene-*p*-sulphonate[8] (55—75% yield). [c] E.e. was determined by h.p.l.c. analysis of the benzoate of (**8**) with a column packed with (+)-poly(triphenylmethyl methacrylate) (elution with methanol).[9] [d] E.e. was determined by h.p.l.c. analysis with a column packed with cellulose tris(3,5-dimethylphenylcarbamate) on silica gel [elution with hexane–ethanol (9 : 1)].[10] [e] Optical rotation values of (**8**) were: $[\alpha]_D^{26}$ +8.71° (*c* 5.18, $CHCl_3$) for $R^1$ = Me, $R^2$ = n-$C_6H_{13}$; $[\alpha]_D^{26}$ −42.7° (*c* 2.36, cyclo-$C_5H_{10}$) for $R^1$ = Me, $R^2$ = Ph; $[\alpha]_D^{26}$ +1.10° (*c* 5.68, cyclo-$C_5H_{10}$) for $R^1$ = H, $R^2$ = Ph. [f] Prepared from $AlBr_3$ with $LiAlD_4$. [g] Based on $[\alpha]_D^{26}$ +1.58° (*c* 7.07, cyclo-$C_5H_{10}$).[11]




(A)

n-$C_6H_{13}$) or (ii) Swern oxidation[7] of (**7**) using dimethyl sulphoxide and oxalyl chloride followed by base ($K_2CO_3$)-catalysed elimination of the chiral auxiliary (for $R^1$ = Me, $R^2$ = Ph; $R^1$ = H, $R^2$ = Ph). After removal of the auxiliary, the crude product was purified by column chromatography and distillation to give the corresponding alcohol (**8**). Table 1 illustrates the results obtained with three different carbonyl systems under various conditions. From these results, it can be seen that (a) the cleavage reaction of acetals (**6**) derived from (−)-(1*S*,3*S*)-(**4**) with hydride reagent produces optically active alcohols (**8**) with good enantiomeric purity; (b) the hydride reagent ($Br_2AlH$) exhibits excellent selectivity; and (c) lower temperature (−15 °C) leads to higher asymmetric induction.

The configuration of the resulting alcohols (**8**) formed by the cleavage of acetals (**6**) with $X_2AlH$ is dependent upon the configuration of (**6**) at the acetal carbon. The sterically less hindered groups ($R^1$) should occupy the axial position in the six-membered transition state (A). These situations parallel the observation of the cleavage reaction of the acetals with other organoaluminium reagents as previously reported.[1]

*Received, 26th August 1986; Com. 1220*

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