Preparation of Optically Active 2,2'-Dihydroxy-1,1'-binaphthyl *via* Microbial Resolution of the Corresponding Racemic Diester

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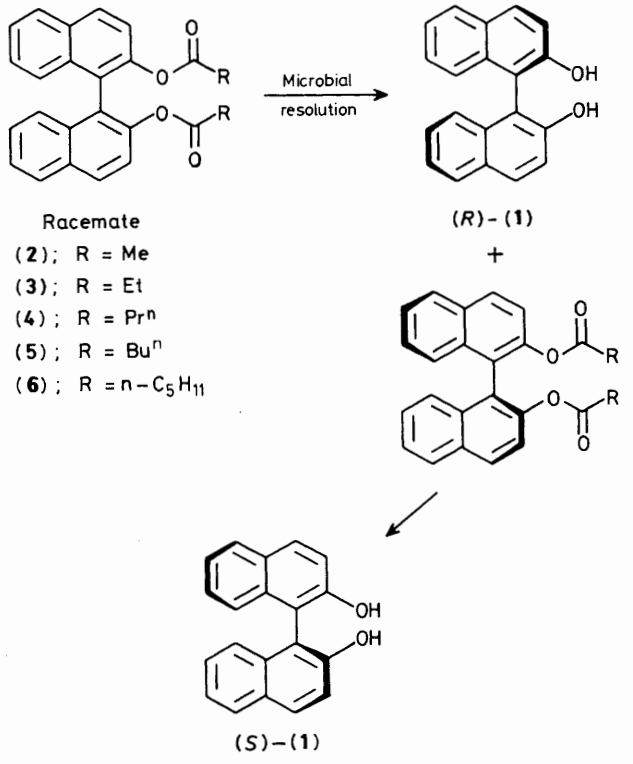
An efficient microbial resolution of 2,2'-dihydroxy-1,1'-binaphthyl has been achieved by exposing the corresponding dibutyrate to *Bacillus sp*; the importance of the size of the ester group for the hydrolysis rate and selectivity is emphasized.

Optically active binaphthyl and biphenyl derivatives with axial chirality have recently been recognized to be an effective constituent of asymmetric reagents[1] such as chiral hydride reagents exemplified by Noyori's BINAL-H.[1a] However, the optically active forms of these axially dissymmetric aromatic compounds have been obtained in most cases by a classical tedious resolution method.[2] We envisaged that resolution of these compounds could be carried out with high efficiency and convenience by use of the esterase activity of micro-organisms or enzymes,[3] and we now describe the successful resolution of 2,2'-dihydroxy-1,1'-binaphthyl (**1**) *via* the selective hydrolysis of diesters of (**1**). This work, to the best of our knowledge, is the first example of the application of microbial (enzymatic) asymmetric hydrolysis for obtaining axially dissymmetric compounds.

In our initial survey the racemic diacetate (**2**) was exposed to pig liver esterase[4] and some micro-organisms which have been employed previously for hydrolysis of acetates. However, even after prolonged incubation periods the hydrolysis of (**2**) did not occur in a reasonable yield.† We therefore screened micro-organisms from soils and isolated more than 30 strains which hydrolyse (**2**) in 20—60% yield on incubation of (**2**) (1 mg/ml) in the nutrient broth medium for ~10 days. The hydrolysis ratio was estimated by g.l.c. analysis of a sample of the crude extract and the enantiomeric excess (e.e.) was measured by h.p.l.c. analysis using a chiral column,[5] CHIRALPAC OP (+), and methanol as eluant for the chromatographically separated diol (**1**). The e.e. of the recovered diester (**2**) was similarly analysed after reduction with lithium aluminium hydride.

Interestingly none of the isolated micro-organisms accumulated the possible mono-acetate intermediate (<5% yield) but afforded the diol (**1**) directly. Further, two types of micro-organism were found, differing in their stereoselectivity; one group (75% of the isolated strains) preferentially hydrolyse the (*S*)-diacetate to give the (*S*)-enriched diol, while the other group exhibited the opposite selectivity and afforded the (*R*)-enriched diol. However, the observed selectivity was not satisfactory for a practical resolution.

Since the selectivity in microbial hydrolysis has been reported to vary with the acyl group of ester substrates,[6] we then prepared a series of diesters (**3**)—(**6**) (propionate—hexanoate) and hydrolysed them with the strains which showed relatively good selectivity in the preliminary experiments with the diacetate (**2**). The results are summarized in Table 1. *Bacillus sp*. L-75, which showed (*S*)-selectivity for the



† *Bacillus subtilis, Rhodotorula glutinis,* and *Saccharomyces rosei* showed some hydrolytic activity.

Table 1. Asymmetric hydrolysis of esters of 2,2'-dihydroxy-1,1'-binaphthyl with micro-organisms.[a]

Medium	Substrate	Hydrolytic ratio (%)	% e.e. of product diol (**1**)	(*R*)/(*S*)
(a) *Bacillus sp.* L-75				
Nutrient broth[b]	(**2**)	43	50	(*S*)
	(**4**)	49	97[d]	(*R*)
	(**5**)	50	96[e]	(*R*)
	(**6**)	8	91	(*R*)
YM[c]	(**3**)	38	25	(*R*)
	(**4**)	54	72	(*R*)
	(**5**)	49	73	(*R*)
	(**6**)	35	96	(*R*)
(b) *Bacillus sp.* K-71				
Nutrient broth	(**2**)	44	43	(*R*)
	(**3**)	41	71	(*R*)
	(**4**)	52	77	(*R*)
	(**5**)	29	77	(*R*)
	(**6**)	13	83	(*R*)

[a] Each diester (54 μM) was incubated at 33 °C for 10 days [2 days preincubation before addition of the substrate as a dimethylformamide (3 ml) solution] in the specified medium (100 ml). [b] Nutrient broth medium (100 ml) contains beef extract (0.3 g), peptone (0.5 g), and Na_2HPO_4 (75 mg). [c] YM medium (100 ml) contains yeast extract (0.3 g), malt extract (0.3 g), peptone (1 g), glucose (1 g), and Na_2HPO_4 (75 mg). [d] 90%e.e. for the recovered (*S*)-diester (**4**). [e] 94%e.e. for the recovered (*S*)-diester (**3**).

diacetate (**2**), showed excellent (*R*)-selectivity for the dibutyrate (**4**) and the dipentanoate (**5**) in the nutrient broth medium, whereas the dipropionate (**3**) and the dihexanoate (**6**) were hydrolysed in poor yield. In the YM medium this micro-organism exhibited a maximum (*R*)-selectivity for the dihexanoate (**6**), while the diacetate was rapidly hydrolysed to the diol (>70% hydrolysis ratio). The other two *Bacillus* strains L-91 and K-91 exhibited similar reactivity and selectivity for the diesters (**2**)—(**6**) as that with L-75. In contrast, the undetermined strain K-71 hydrolysed the diesters (**2**)—(**6**) to give the (*R*)-enriched diol.

These data clearly indicate the importance of the size of acyl group as well as the medium to get maximum selectivity in the kinetic resolution of the diester of (**1**). The generally employed acetates are not necessarily the best substrate. For practical purposes dibutyrate‡ appeared to be most suitable since precipitation becomes a problem for larger diesters.

We are currently examining the applicability of this method for other axially dissymmetric aromatic compounds.

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‡ The dibutyrate (**4**) (140 mg) was incubated with *Bacillus sp.* L-75 for 11 days in the nutrient broth medium (100 ml) as described for Table 1. Extraction (ethyl acetate) and silica gel column chromatographic separation afforded the recovered (*S*)-dibutyrate (72 mg, 51% yield, 91% e.e.) and the (*R*)-diol (**1**) (45 mg, 48% yield, 97% e.e.).

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