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TETRAHEDRON: *ASYMMETRY*

Access to optically active 2,2′-dihydroxy-6,6′-dimethoxy-1,1′-biphenyl by a simple biocatalytic procedure

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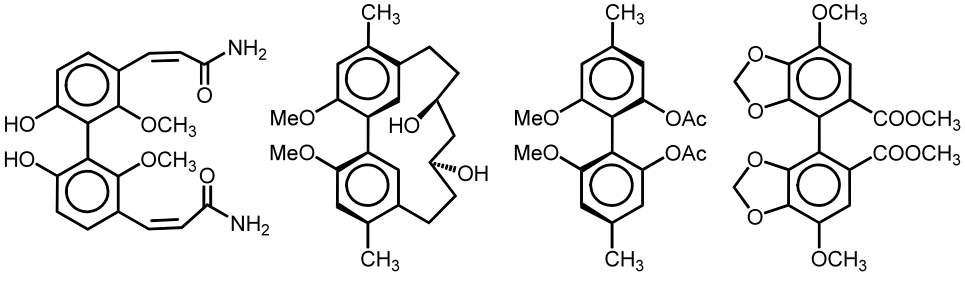
Abstract—Lipase from *Pseudomonas cepacia* was found to catalyze acetylation in *tert*-butyl methyl ether of the title alcohol **1**. The action of four different *P. cepacia* preparations was compared, all possessing high steric recognition, that results in an efficient kinetic resolution of this atropisomeric biphenyl.

The geometrical possibilities offered by chemical transformation of the biphenyl skeleton makes it a versatile building block in drug synthesis, as a ligand skeleton in homogeneous catalysis and as redox-switches in materials science.[1] Biphenyls can be readily recognised as configurationally stable analogues of the widely used 1,1′-binaphthyl-2,2′-diol (BINOL).

The growing number of *ortho*-hydroxylated biphenyls isolated from natural sources [e.g. cinnamide dimer **4** and alnusdiol (a*S*,*S*,*S*)-**5**] makes the biphenol unit the backbone for the preparation of biologically active compounds.[2] Natural occurring biphenyls, often having simple structures and are present in enantiopure form, possess biological activities and constitute important starting materials for the synthesis of antibiotics,[3] inhibitors of HIV reverse transcriptase,[2c] antimicrobial agents (compound a*S*-**6**),[4] liver-protecting agents (compound **7**)[5] and, recently, synthetic ionophores to control the binding affinity to cations.[1c,6]

According to the functional groups attached to the aromatic ring, the preparation of hydroxylated biphenyls involves different synthetic strategies which provide symmetrical and unsymmetrical derivatives.[7] Despite the large number of synthetic procedures in literature, only a few reactions allow biphenols to be prepared as atropoenantiomers in high enantiomeric excess and chemical yield.[8]

Although some resolution methodologies have been developed to resolve racemic BINOL, few cases have been reported in literature for the preparation of optically active hydroxylated biphenyls. As far as we know,



4 (a*S*,*S*,*S*)-**5** (a*S*)-**6** **7**

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for this class of compounds only chemical resolution procedures[9] are available and the alternative use of biocatalysed procedures could be of advantage. In this context, although lipases have been widely employed in the discrimination of the enantioforms of chiral compounds, their use in the kinetic resolution of biaryls with axial chirality is very poor and the few reported examples are restricted to binaphthyl derivatives. Oda et al.[10] at first, and Juarez-Hernandez et al.[11] recently, obtained good results in the stereoselective resolution of the racemic BINOL using lipase from *Pseudomonas* sp. or *Pseudomonas fluorescens* that both catalyze the mono acylation of phenolic groups. On the other hand attempts to perform enantioselective lipase-catalyzed esterifications of 1,1′-binaphtyl-2,2′-dicarboxylic acid failed; however, this compound was obtained in optically active form by lipase *Humicola* sp. catalysed resolution of its precursor 2,2′-bis(hydroxymethyl)-1,1′-binaphthyl and subsequent chemical oxidation.[12] Finally, Aoyagi and Izumi[13] demonstrated that amidation with *P. aeruginosa* lipase of 1,1′-binaphthylamines was ineffective in the case of amino groups directly bonded to the aromatic ring, whereas the enzymatic resolution was successful when the amino group was located on the alkyl side chain.

Surprisingly the lipase's behaviour in the steric recognition of atropisomeric forms of simple biphenyl systems has not been reported.

Because of its remarkable synthetic potential as a starting material[8a,14] in the preparation of molecules with axial chirality we have considered 2,2′-dihydroxy-6,6′-dimethoxy-1,1′-biphenyl, (±)-**1**,[15] developing a biocatalytic procedure for its enantiomeric separation and the results obtained are reported herein.

First we attempted the transesterification of (±)-**1** in organic solvents catalysed by different lipases from *Mucor miehei*, *Candida cylindracea* and *P. cepacia*. Among the mentioned enzymes investigated only lipase from *P. cepacia* (PSL) was found to catalyze efficiently the acetylation reaction of biphenol (±)-**1** into corresponding acetyl derivative (a*R*)-**2**. Since the crude lipase was able to catalyze the reaction with good steric recognition but with a slow rate, we decided to extend our investigation to three different PSL preparations, two commercially available from Amano, the third one prepared in our laboratory by standard procedure (Table 1).[16]

All the experiments were performed using *t*-butyl methyl ether (*t*-BME) as the solvent and vinyl acetate as the acyl donor.[17] Under these conditions commercial PSL-C (PSL adsorbed on ceramic) gave the best results in terms of reaction rate associated with an appreciable enantiodiscrimination ($E=74$); PSL-D (PSL adsorbed on Kaolin) exhibited a comparable enantioselectivity but a lower catalytic efficiency, according to the specific activity of these commercial lipase preparations.[18] PSL adsorbed on Celite was able to catalyze the esterification reaction with excellent enantioselectivity ($E>100$) but with a too low reaction rate. It must be noted that all the enzymes catalyzed the mono-esterification of (±)-**1**, to give (a*R*)-**2** that does not possess the C_2-symmetry of the parent. Under no circumstances was the presence of diester seen in the reaction medium. This behaviour can be probably explained considering that

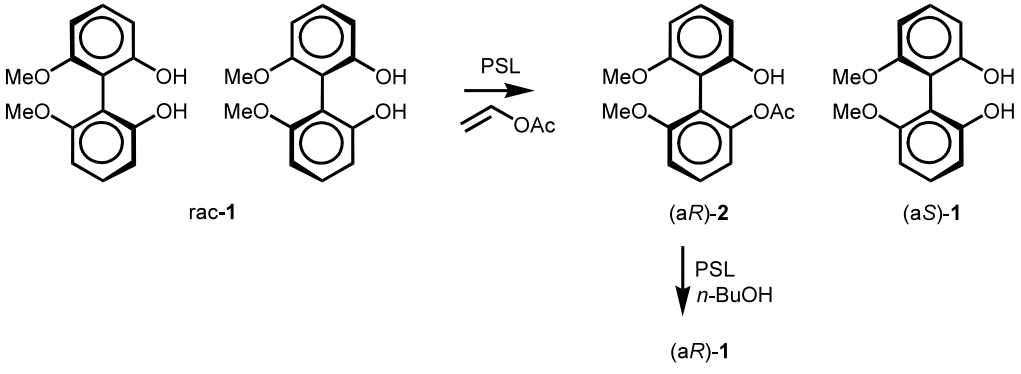
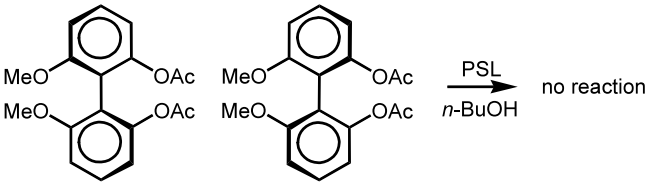


Table 1. Esterification of rac-**1** with PSL immobilized on different supports[a]

Lipase preparation	Support	Time (days)	Conv. %[b]	**1**, e.e. %[c]	**2**, e.e. %[c]	*E*
PSL	None	2	7	7	>98	>100
PSL-C[d]	Surface of ceramic	1	51	96	90	74
PSL-D[d]	Kaolin minerals	2	44	75	94	73
PSL-Celite[e]	Diatomaceous earth	3	41	67	98	>100

[a] All reactions were performed in *t*-BME at a substrate concentration of 20 mM, with 20 mg/ml of immobilized enzyme, vinyl acetate 1.5 equiv. The reactions were shaken at 300 rpm and 45°C.
[b] Conversions were measured by ^{1}H NMR analysis.
[c] E.e. were determined by chiral HPLC analysis on Chiralcel® OD column eluting 90:10 hexane:2-propanol mixture.
[d] See Ref. 18.
[e] See Ref. 16.

the first acetyl group exercises steric hindrance, supported by the atropisomeric nature of the molecule, making the second vicinal hydroxyl group unavailable for esterification.[19] This hypothesis was confirmed by the unreactivity of the chemical ester (±)-**3** when alcoholysis reactions in the presence of PSL-preparations and *n*-butanol (*n*-BuOH) were attempted. Whereas the alcoholysis of monoester (a*R*)-**2** in the presence of *n*-BuOH and PSL-C afforded (a*R*)-**1** in quantitative yield.



rac-**3**

In conclusion, lipase from *P. cepacia*, in the adopted conditions, is a useful biocatalyst to realize the efficient enantiomeric resolution of (±)-**1** in high enantiomeric excess and chemical yields. The use of different preparations of this lipase always led to satisfactory enantioselectivity despite of a reasonable variation of the reaction rate. Since the lipase catalysis in the esterification of (±)-**1** occurs specifically with a monoacylation of the substrate, this biocatalytic procedure is successful in also providing the desymmetrization of the obtained ester.

Further studies concerning the effect of the ester group on the regioselective functionalization of biphenyl (a*R*)-**2**, as well as the use of the enzymatic procedure to resolve other hydroxylated biphenyls are being carried out in our laboratories.

Acknowledgements

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17. **Compound (a*S*)-1**: Obtained from a reaction involving 200 mg (0.8 mmol) of (±)-**1** dissolved in *t*-BME (150 mL) containing vinyl acetate (1.5 equiv.) and PSL-C (800 mg). The reaction was shaken at 45°C and stopped after 42 h reaching 53% of conversion. Chromatographic purification on Lichroprep® Si 60 eluting with 95:5 mixture of

CH_2Cl_2:Et_2O furnished 82 mg of (a*S*)-**1** (41% yield), with 98% e.e. (by chiral HPLC analysis). The absolute configuration of biphenol was assigned by comparing its specific rotation to the literature value for (a*S*)-(−)-2,2′-dihydroxy-6,6′-dimethoxy-1,1′-biphenyl.[15a]

Compound (a*R*)-2: Obtained from a reaction involving 200 mg (0.8 mmol) of (±)-**1** dissolved in *t*-BME (150 ml) containing vinyl acetate (1.5 equiv.) and PSL-Celite (800 mg) and incubated in shaker at 45°C. The reaction was stopped after 72 h reaching 41% of conversion. Chromatographic purification as above gave 88 mg (0.30 mmol) of ester (a*R*)-**2** (38% yield) with 98% e.e.: $[\alpha]_D = +91.2$ (*c* 0.7, $CHCl_3$). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.95 (3H, s), 3.71 (3H, s), 3.78 (3H, s), 6.55 (1H, d, $J = 8.2$ Hz), 6.66 (1H, d, $J = 8.2$ Hz), 6.84 (1H, d, $J = 8.2$ Hz), 6.93 (1H, d, $J = 8.2$ Hz), 7.24 (1H, t, $J = 8.2$ Hz), 7.42 (1H, t, $J = 8.2$ Hz). ^{13}C NMR (100.03 MHz, $CDCl_3$) δ 20.43, 55.99, 56.29, 103.17, 109.13, 109.16, 109.23, 115.07, 115.21, 129.76, 130.01, 150.73, 154.61, 158.00, 158.64, 169.66.

18. The enzyme activity reported by Amano for lipase PS-C and for PS-D is 30U/mg and 8U/mg, respectively.
19. In the same esterification conditions PSL-C, PSL-D and PSL-Celite transformed 2,2′-dihydroxy-1,1′-biphenyl in the corresponding diacetyl derivative; as well as the alcoholysis reactions on 2,2′-diacetoxy-1,1′-biphenyl were successful.