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A rapid 1,2-dihydroxylation of alkenes using a lipase and hydrogen peroxide under microwave conditions

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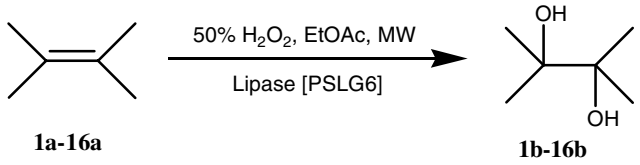
Abstract—The combined advantages of using an enzyme immobilized lipase from *Pseudomonas* sp [PSLG6], hydrogen peroxide, ethyl acetate and microwave irradiation for the dihydroxylation of olefins are reported.

1,2-Dihydroxy compounds are important intermediates for the preparation of different pharmaceuticals such as antagonists of central and peripheral dopamine receptors,[1] fragrants,[2] cosmetics,[3] photographic plates[4] and lubricants[5] and also as additives[6] in various synthetic reactions. Generally 1,2-diols are prepared either by acid[7] catalyzed hydrolysis of epoxides in the presence of metal oxides, transition metal complexes[8] or epoxide hydrolases,[1,9] dihydroxylation of olefins with potassium permanganate,[10] osmium tetroxide,[11] zeolite catalysts,[12] or by reduction of α-hydroxy ketones and diketones.[13] However, from the point of view of atom efficiency, the performance of these reagents is very poor. Further, over-oxidation with consequent cleavage of C–C bonds in certain cases, poor selectivity, long reaction times[14] and use of toxic solvents are some of the associated problems. Hence, the controlled use of hydrogen peroxide for 1,2-dihydroxylation of olefins under specific conditions provides a better solution.[15]

Lipase assisted epoxidations using peroxides and acids or esters is an attractive reaction in clean chemistry research areas.[16] In continuation of our recent work[17] on epoxidation using such methodologies, we report here a rapid method for direct 1,2-dihydroxylation of various alkenes using immobilized lipase from *Pseudomonas* [PSLG6], 50% hydrogen peroxide and ethyl acetate in a microwave in a single step (Scheme 1).[18]



Scheme 1. Lipase catalyzed dihydroxylation of olefins under microwave irradiation.

The yields of the 1,2-diols ranged from 70% to 90% (Table 1). The advantages of our method are: (i) it is metal free; (ii) is rapid; (iii) gives high yields; (iv) the catalyst can be recycled four times and; (v) the method is simple and safe.

A control experiment was carried out to check the requirement for lipase in the reaction. In the absence of lipase, no diol formation occured.

The reaction proceeds through formation of an epoxide (Scheme 2),[19] however, no intermediate epoxide could be isolated from the olefins **1a**–**16a**. In the cases of cholesterol and stigmasterol **17a** and **18a**, the reaction is noteworthy. The isolated double bond in stigmasterol **18a** at C-22 remained unaffected under the reaction conditions, whilst the sterically hindered double bonds at C-5,6 in both cholesterol **17a** and stigmasterol **18a** were epoxidized to give 5α,6α-epoxides **17b** and **18b** (Scheme 3). The hydroxyl at C-3 of cholesterol **17a** and stigmasterol **18a** probably facilitated epoxide formation. Epoxides **17b** and **18b** were stable and did not undergo ring opening to the diols.

The dihydroxylation of cyclohexene and 1-phenylcyclohexene **12a** and **13a** under the above conditions

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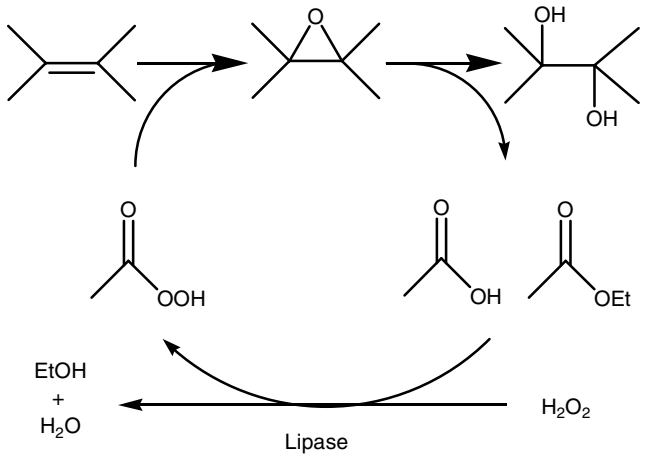
Table 1. 1,2-Dihydroxylation of olefins with 50% H_2O_2 and ethyl acetate in the presence of [PSLG6] under microwave irradiation[a]

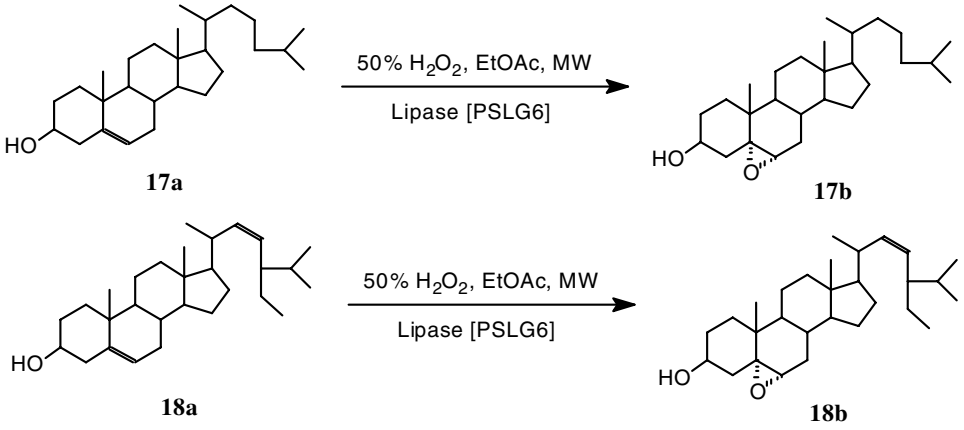
Entry	Substrates **1a–18a**	Products[b] **1b–18b**	Time (min)	Yield[c] (%)
1	Styrene	1-Phenyl-1,2-ethanediol	6	76
2	4-Cl–styrene	4-Cl–phenyl-1,2-ethanediol	5	90
3	3-Cl–styrene	3-Cl–phenyl-1,2-ethanediol	5	85
4	2-Cl–styrene	2-Cl–phenyl-1,2-ethanediol	6	80
5	4-Br–styrene	4-Br–phenyl-1,2-ethanediol	5	83
6	3-Br–styrene	3-Br–phenyl-1,2-ethanediol	5	81
7	2-Br–styrene	2-Br–phenyl-1,2-ethanediol	6	79
8	4-Nitrostyrene	4-Nitrophenyl-1,2-ethanediol	7	85
9	3-Nitrostyrene	3-Nitrophenyl-1,2-ethanediol	7	83
10	2-Nitrostyrene	2-Nitrophenyl-1,2-ethanediol	7	80
11	4-MeO–styrene	4-MeO–phenyl-1,2-ethanediol	10	77
12	Cyclohexene	*trans*-Cyclohexane-1,2-diol	8	87
13	1-C_6H_4-1-Cyclohexene	*trans*-1-Phenylcyclohexane-1,2-diol	10	80
14	α-Me–styrene	1-Me-1-phenyl-1,2-ethanediol	10	70
15	1-Hexene	1,2-Hexanediol	10	72
16	*trans*-2-Hexene	*trans*-2,3-Hexanediol	10	83
17	Cholesterol	Cholest-5α,6α-epoxy-3β-ol[18,20I]	10	85
18	Stigmasterol	Stigmast-5α,6α-epoxy-3β-ol[18,20K]	10	83

[a] The reactions were run with olefin (8–10 mmol), 50% H_2O_2 (2.5 mL, 36 mmol), ethyl acetate (5 mL) and lipase PSLG6 (20 mg) under microwave irradiation for 5–10 min.
[b] The products were characterized from their respective IR, NMR and mass spectroscopic data and by comparison with the literature data.[20]
[c] Isolated yields of products.



Scheme 2. Lipase catalyzed dihydroxylation of olefins under microwave irradiation.

produced *trans*-1,2-cyclohexanediol **12b** and *trans*-1-phenylcyclohexanediol **13b** in 87% and 80% yields, respectively. Interestingly, under microwave irradiation (150 W) the immobilized lipase [PSLG6] was not denatured and could be recycled in subsequent runs which is in agreement with the earlier observations.[15] The conversion was found to occur best on exposure to MW irradiation (150 W) for 5–10 min whereby the reaction temperature was about 60 °C (measured in a conventional manner by stopping the exposure). The microwave irradiation increases the reaction rate and decreases inactivation of the enzyme during the reaction.[15] When the reaction was carried out under conventional conditions at reflux, it required more than 20 h for completion and the yield of the diols obtained were found to be lower in comparison. The product diols in all the cases were accompanied by 5–8% of the 2-acetyloxy derivatives formed through transesterification with ethyl acetate in the presence of lipase. Similar results



Scheme 3. Lipase catalyzed epoxidation of sterol substrates under microwave irradiation.

were observed when the reaction was carried out using commercially available immobilized lipase from *Candida antarctica* [Novozyme (435)], however, in lower yields.

In conclusion, a simple, safe and environmentally benign method for the direct 1,2-dihydroxylation of olefins was developed that could be carried out within a few minutes.

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18. *Typical procedure:* A 50 mL conical flask was charged with styrene **1a** (1.04 g, 10 mmol), aqueous hydrogen peroxide (50%, 2.5 mL, 36 mmol), ethyl acetate (5 mL) and lipase [PSLG6] (20 mg). The mixture was irradiated at 150 W in a microwave oven (EMS-820 Precision Pulsed Laboratory Microwave Oven) for 5 min. Air was purged through the reaction mixture in order to ensure thorough mixing of the reactants inside the MW chamber. The mixture was then allowed to cool and ethyl acetate (10 mL) was added. The mixture was then filtered and the residual solid immobilized lipase was washed with 8:2 acetonitrile–water mixture and dried for subsequent use. The filtrate containing both the aqueous and organic layer was separated. The organic layer was washed with Na_2SO_3 solution (20%, 10 mL), $NaHCO_3$ solution (5%, 20 mL × 2) and then with water (20 mL × 2), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford 1-phenyl-1,2-ethanediol (1.24 g, 9 mmol) as a white solid; mp 67 °C (lit.,[20b] 66–67 °C). The same reaction was carried out with various alkenes in a similar manner to give the corresponding diols **1b**–**16b** and epoxides **17b** and **18b**.
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