

ENZYMATIC RESOLUTION OF 2,3-EPOXYALCOHOLS,  
INTERMEDIATES IN THE SYNTHESIS OF THE GYPSY MOTH SEX PHEROMONE

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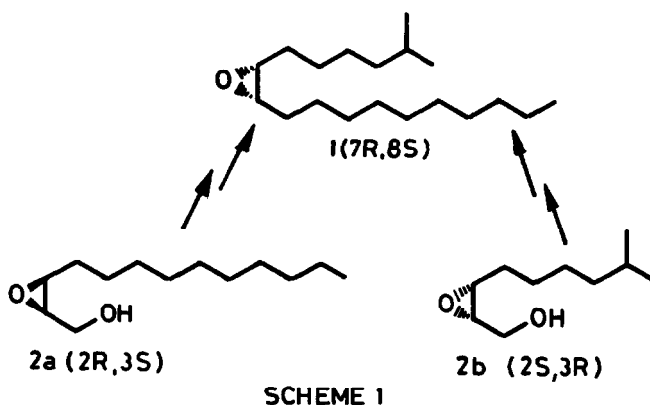
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Abstract: An efficient resolution of 2,3-epoxyalcohols 2a-b were obtained both by enzymatic hydrolysis and transesterification in organic solvent : (2S,3R) 2b and (2R,3S) 2a thus obtained are chiral synthons for the synthesis of (+)-Disparlure 1.

Disparlure, (cis-7,8-epoxy-2-methyloctadecane) 1 was identified as the female-produced sex pheromone of the gypsy moth, *Lymantria dispar* L.<sup>1</sup>.

Extensive investigations proved that the dextro enantiomer (cis-7R,8S-epoxy-2-methyloctadecane) is more active than the racemate<sup>2</sup>.

Recently Sharpless<sup>3</sup> and Mori<sup>4</sup> reported new synthesis of (+)-disparlure starting from the optically active epoxyalcohols 2a and 2b (SCHEME 1) prepared by asymmetric epoxidation.



In our attempt to find a simple method for large scale preparations of this pheromone we decide to study a new route to the optically active epoxyalcohols 2a and 2b using hydrolytic enzymes in water<sup>5</sup> and, for the first time on this kind of substrates, in organic solvents<sup>6</sup>.

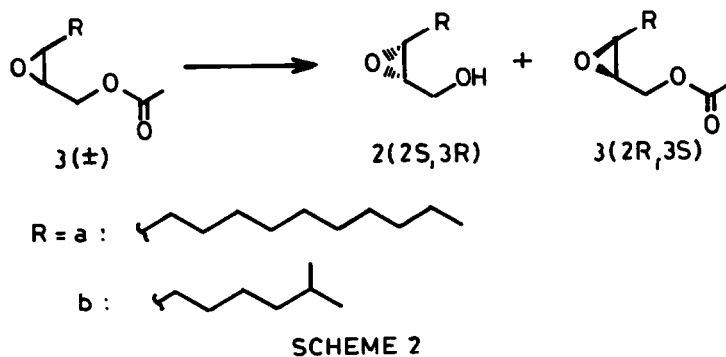
Acetates of racemic epoxyalcohols 3a-b were subjected to stereoselective hydrolysis using Lipase (EC 3.1.1.3. Sigma Type II, from porcine pancreas) (SCHEME 2).

The reactions were carried out at pH 7.6, T=25°C and stopped at different degrees of conversion. The pH was maintained constant by addition of 0.5N aqueous NaOH. Alcohols and unhydrolyzed esters were recovered by extraction with ethyl acetate and purified by chromatography on silica gel eluting with hexane-ethyl acetate 95-5 v/v.

The absolute configurations and the enantiomeric excesses (ee's) are summarized in Table 1.

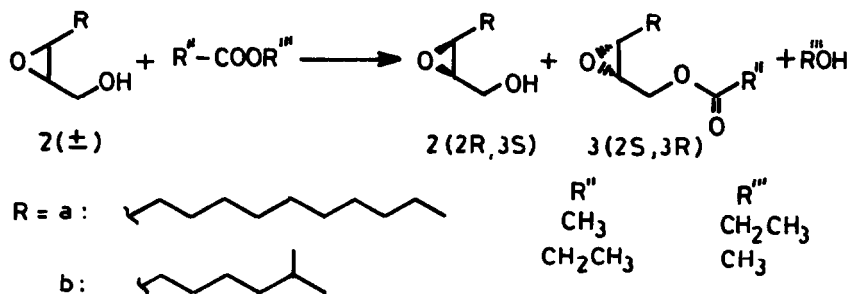
Enzymatic hydrolysis of racemic esters 3a-b afforded the epoxyalcohols of 2S, 3R configuration.

Since 7R,8S enantiomer of disparlure 1 is the most active one, only 2b can be utilized as intermediate in the synthesis of this pheromone.



In order to prepare 2a-b with the configuration 2R,3S we studied the lipase catalyzed transesterification which is complementary to the enzymatic hydrolysis with respect to the stereochemistry of the final products\* (SCHEME 3).

The reactions were carried out in ethyl acetate or methyl propionate employed both as acylating agents and as reaction media with the same enzyme used in the hydrolytic approach.



Powdered lipase was added to a solution of racemic 2a-b in ethyl acetate at 40°C and the suspension was shaken in an orbital shaker at 200 rpm; periodically 1µl aliquots were withdrawn and analyzed by gas chromatography. The reactions were stopped at different degrees of conversion, the enzyme filtered off and the crude mixtures were worked up (TABLE 1). The recovered enzyme could be reused and no significant losses of activity were observed after repeating the experiment.

Table 1. Enzymatic resolution of epoxyalcohols 2a-b and 3a-b.

Racemic substrate	Solvent	Time (h)	% conv.	Yield %	$[\alpha]_D^{20}$	Alcohol ee% <sup>a</sup>	config.
3a	H <sub>2</sub> O	4	43	36	+5.20 <sup>b</sup>	67.2	2S,3R
3a	H <sub>2</sub> O	2.5	38	32	+7.83	>95	2S,3R
3b	H <sub>2</sub> O	2	40	37	-2.80 <sup>c,d</sup>	87.5	2S,3R
3b	H <sub>2</sub> O	1.5	25	20	-3.20	>95	2S,3R
2a	AcOEt	20	40	55	-3.91 <sup>b,e</sup>	60.0	2R,3S
2a	AcOEt	30	65	31	-7.90	>95	2R,3S
2a	MeProp	48	45	50	-4.82	61	2R,3S
2b	AcOEt	24	60	36	+3.20 <sup>c</sup>	>95	2R,3S

a: enantiomeric excesses were determined by capillary gas chromatography of Mosher's esters<sup>7</sup>;

b:  $[\alpha]_D^{20}$  (C=1, EtOH<sub>100%</sub>);

c:  $[\alpha]_D^{20}$  (C=2, CHCl<sub>3</sub>);

d: lit.<sup>4</sup>  $[\alpha]_D^{20} = -2.55$  (C=2.43, CHCl<sub>3</sub>);

e: lit.<sup>8</sup>  $[\alpha]_D^{20} = -7.8$  (C=1, EtOH<sub>100%</sub>)

Epoxyalcohols 2a and 2b were then used as chiral syntons in the (+)-disparlure synthesis according to Sharpless<sup>9</sup> and Mori<sup>10</sup>.

Field tests of these pheromones are under way.

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