Enzyme Discrimination between Conformational Enantiomers as a Means of Effecting Asymmetric Syntheses

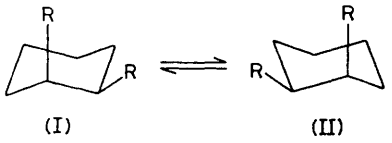
By H. BRUCE GOODBRAND and J. BRYAN JONES*
(*Department of Chemistry, University of Toronto, Toronto, Ontario, Canada* M5S 1A1)

Summary Enzymes have been used to effect asymmetric syntheses with chiral molecules which are racemic at room temperature since their conformers are enantiomeric; stereospecific horse liver alcohol dehydrogenase-catalysed oxidations in high (80%) yields of *cis*-1,2-bis-(hydroxymethyl)cyclohexane and its Δ^4-analogue to (1*S*,-2*R*)-*cis*-2-hydroxymethylcyclohexanecarboxylic acid lactone (optically pure) and the corresponding (1*S*,6*R*)-Δ^3-lactone (85% optically pure), respectively, have been carried out.

THE asymmetric synthesis of chiral molecules whose conformers are enantiomeric, such as (I) and (II),[1,2] is particularly challenging, since, owing to their conformational mobility, they exist as racemates at room temperature† and cannot be resolved unless the ring inversion barrier is

† The term atropisomerism has also been used in discussions of conformational enantiomers (refs. 2 and 3).

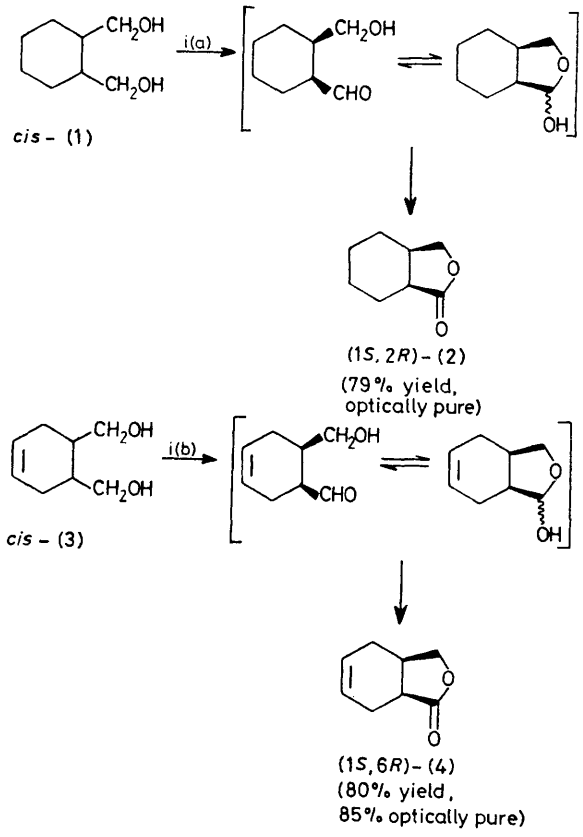
exceptionally high.[2] In principle, the individual conformers are resolvable using low temperature techniques.[2,3] However, up till now, direct synthetic transformations of one enantiomer *only* of such compounds have not been possible. Enzymic catalysis offers a solution to this problem since conformationally mobile substrates are, in effect, 'frozen' when Michaelis enzyme–substrate (ES) complexes are formed. Thus, for conformers such as (I) ⇌ (II), enzyme-catalysed transformations will occur stereospecifically if one of the two diastereomeric ES complexes is significantly preferred.‡ Furthermore, a process of this type should occur in high yield since it would be accompanied by a continuous displacement of the conformational equilibrium in the preferred direction. We now present a demonstration of the effectiveness of this new approach to asymmetric synthesis.



(I) (II)

Preparative-scale (2 g of substrate) HLADH§-catalysed oxidations of the *cis*-1,2-diols (**1**) and (**3**) were effected by the standard procedure[4] employing FMN-mediated recycling[5] of catalytic quantities of the NAD^+ coenzyme (Scheme). For both diols, the oxidations gave excellent yields and were highly stereoselective for the hydroxymethyl groups attached to the *S*-centres with the initial aldehyde products undergoing further enzyme-mediated oxidation in their cyclic hemiacetal form[4] to give the corresponding lactones (1*S*,2*R*)-(**2**) and (1*S*,6*R*)-(**4**) directly. The absolute configuration and optical purity of (1*S*,2*R*)-(**2**) was established by its hydrolysis and epimerisation to (1*R*,2*R*)-*trans*-2-hydroxyethylcyclohexanecarboxylic acid[6] followed by $LiAlH_4$ reduction to (1*R*,2*R*)-*trans*-1,2-bis(hydroxymethyl)cyclohexane.[7] The Δ^3-lactone (1*S*,6*R*)-(**4**) was similarly correlated with (4*R*,5*R*)-*trans*-4,5-bis(hydroxymethyl)cyclohexene[8] and by catalytic hydrogenation to (1*S*,2*R*)-(**2**).

The stereospecificity observed is in accord with that expected from analysis of the conformers of (**1**) and (**2**) in terms of the diamond lattice section of the enzyme's active site.[4] The lattice model also indicates that the hydroxymethyl groups oxidised are axially oriented in the ES-complex.



SCHEME. i, HLADH, pH 9, 20 °C; (a) 4 days, NAD^+ recycling, (b) 3 days, NAD^+ recycling.

The results described illustrate the viability of the approach as a practical technique for asymmetric synthesis.

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‡ This type of enzymic discrimination parallels that documented for *meso*-compounds (ref. 1, pp. 134, 135, and 189—193). However, conformationally enantiomeric molecules are not *meso* compounds in the classical sense since the individual conformers, *e.g.* (I) and (II), do not possess mirror-image symmetry.

§ Abbreviations: HLADH, horse liver alcohol dehydrogenase (E.C. 1.1.1.1); FMN, flavin mononucleotide; NAD^+, nicotinamide adenine dinucleotide (oxidized form).

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