Preparation of Useful Chiral Lactone Synthons *via* Stereospecific Enzyme-catalysed Oxidations of *meso*-Diols

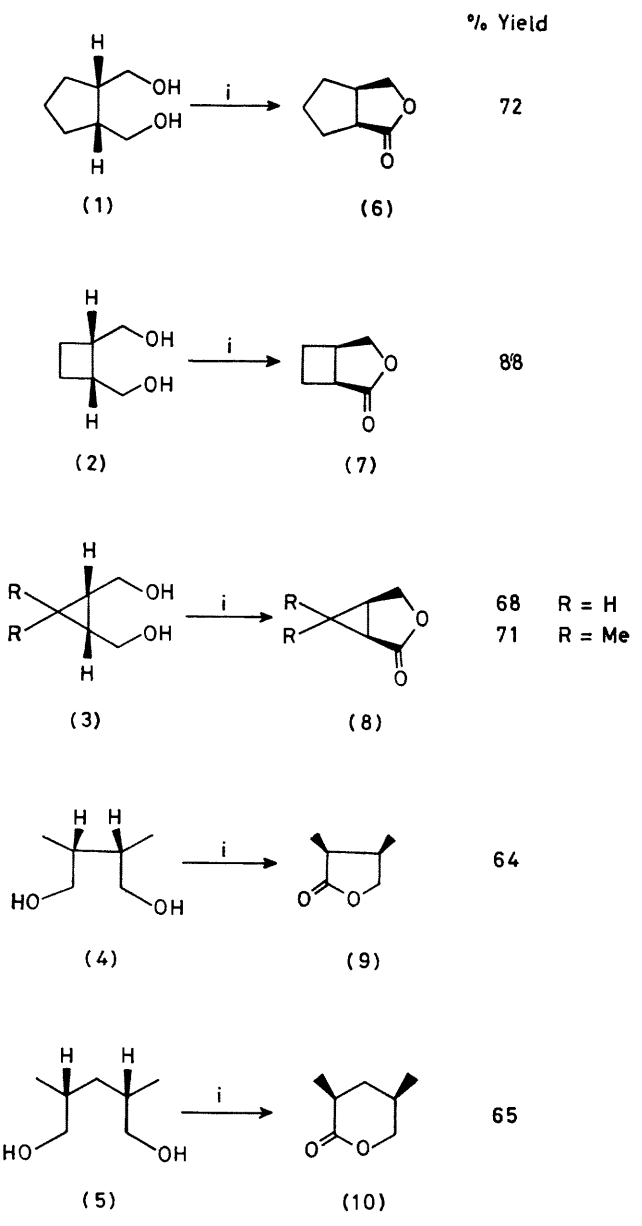
By IGNAC J. JAKOVAC, GEORGE NG, KAR P. LOK, and J. BRYAN JONES*
(*Department of Chemistry, University of Toronto, Toronto, Ontario, Canada* M5S 1A1)

Summary Horse liver alcohol dehydrogenase-catalysed oxidations of symmetrical acyclic and cyclic *meso*-diol substrates give chiral γ- and δ-lactones in high yields and of 100% enantiomeric excess and provide access to a broad range of useful synthons of value in asymmetric syntheses of natural products.

THE unique opportunities provided by enzymes in asymmetric synthesis are becoming increasingly recognised and exploited; of particular value is the ability of many enzymes to catalyse stereospecific transformations of symmetrical substrates into chiral products.[1] A powerful illustration was provided recently by the stereospecific, high-yield, horse liver alcohol dehydrogenase (E.C.1.1.1.1.) (HLADH)-catalysed oxidation of the *meso*-substrate *cis*-1,2-bis-(hydroxymethyl)cyclohexane to (1*S*,2*R*)-*cis*-2-hydroxymethylcyclohexane carboxylic acid lactone.[2]

Preparative-scale (up to 2 g of substrate) HLADH-catalysed oxidations of the *cis*-diols (**1**)—(**5**)[3]† were effected by the standard procedure[4] using flavin mononucleotide (riboflavin phosphate)-recycling[5] of catalytic amounts of the nicotinamide adenine dinucleotide (NAD^+) coenzyme. For each of the cyclic or acyclic diols (**1**)—(**5**), the oxidations were stereospecific for the hydroxymethyl-groups attached to chiral centres of the same absolute configuration types,‡ with the corresponding hydroxy-aldehydes formed initially undergoing further HLADH-catalysed oxidation[2,4] to give the lactones (**6**)—(**10**) of 100% enantiomeric excess (e.e.) in excellent yields. The yields recorded in the Scheme are of the isolated, purified products.§ The optical purities of the lactones (**6**)—(**10**) were established by n.m.r. spectroscopy,[6] and their absolute configurations by conversion into, or comparison with, known reference compounds, as follows: (1*S*,2*R*)-(**6**), $[\alpha]_D^{20}$ + 96·9° (*c* 1, $CHCl_3$), into (−)-(1*R*,2*R*)-methyl 2-methylcyclopentanoate;[7] (1*S*,2*R*)-(**7**), $[\alpha]_D^{20}$ + 118·7° (*c* 10, $CHCl_3$), into (−)-(1*R*,2*R*)-*trans*-bis(hydroxymethyl)-cyclobutane;[8] (1*S*,2*R*)-(**8**; R=H), $[\alpha]_D^{20}$ −61·8° (*c* 6·6, $CHCl_3$), by c.d. comparison with (−)-(1*R*,2*S*)-(**8**; R=Me); (1*R*,2*S*)-(**8**; R=Me), $[\alpha]_D^{20}$ −36·6° (*c* 13·8, $CHCl_3$), into (+)-(1*R*,2*S*)-*cis*-methylchrysanthemate;[9] (2*S*,3*R*)-(**9**), $[\alpha]_D^{20}$ + 39·9° (*c* 11·3, $CHCl_3$), into (+)-(2*S*)-ethyl 2,3-dimethylbutanoate;[10] and (2*S*,4*R*)-(**10**), $[\alpha]_D^{20}$ + 39·1° (*c* 10, $CHCl_3$), into (−)-(2*S*)-2,4-dimethylpentanol.[10]

The above results demonstrate the HLADH-catalysed oxidation of *meso*-diols to be an efficient and versatile route to a broad structural range of enantiomerically pure chiral lactones. Such compounds, which are not readily available



SCHEME. i, HLADH, 20 °C, pH 9, Nad^+-recycling, 3 days. 100% E.e. was achieved in each case.

† All new compounds reported have been fully characterised.

‡ *I.e.* *S*, except for (**3**; R=Me) for which, as a consequence of the *R*/*S* nomenclature rules, the hydroxymethyl group oxidised is the one attached to the *R*-centre.

§ The reaction mixtures obtained from the oxidations of (**4**) and (**5**) contained some of the initially formed hemiacetal precursors of (**9**) and (**10**), respectively. These were readily converted into the corresponding lactones by silver carbonate oxidation (ref. 4).

via traditional chemical approaches, are valuable synthons for a number of important natural products For example, (**10**) could be a key intermediate for the macrolide antibiotic methynolide [11] Lactone (**10**) can also be readily elaborated into the Dutch elm bark beetle pheromone multistriatin,[12] as may (**8**, R=Me) into pyrethroids[13] and (**7**) into the boll weevil pheromone grandisol [14]

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