The unsaturated keto aldehyde (0.0494 g, 0.185 mmol) was dissolved in dry tetrahydrofuran (1.0 ml) and ethylene glycol (0.0115 g, 0.185 mmol), dried over $CaSO_4$, and distilled from sodium metal onto activated molecular sieves type 13X). A few crystals of calcium sulfate (Drierite, 8 mesh) were added along with 2 μl of concentrated sulfuric acid. The mixture was then allowed to stand in a refrigerator at 5 °C overnight. The reaction was then quenched with solid sodium bicarbonate. The mixture was poured into saturated sodium bicarbonate solution (10 ml) and ether (50 ml). The ether layer was separated, and the aqueous layer was extracted with ether (3 × 10 ml). The combined ethereal extracts were washed with water (4 × 5 ml) and saturated sodium chloride solution (10 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo. The crude keto acetal was chromatographed on silica gel-60 (20 g) using 60% ether:40% pet-ether (bp 30–60 °C) eluent collecting 12-ml fractions. Fractions 10–13 were combined to give 0.0513 g (89.5%) of keto acetal **15b:** bp 93–95 °C (external temperature, 0.05 mm); IR ($CHCl_3$) 1720 (CO_2CH_3), 1670 cm^{-1} (CO); NMR ($CDCl_3$) δ 0.90 (s, 3, CH_3), 1.23 (s, 3, CH_3), 3.67 (s, 3, OCH_3), 3.96 (bs, 4, OCH_2CH_2O), 5.55 (s, 1, CHO_2), 7.20 ppm (dofd, J = 2 and 6 Hz, 1, C=CH). Anal. ($C_{17}H_{24}O_5$) C, H.

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(27) This reaction must be conducted in a well-ventilated hood; the chemist should wear rubber gloves during the workup because both hexamethylphosphoramide and chloromethyl methyl ether are carcinogens.

Asymmetric Syntheses via Enantiotopically Selective Horse Liver Alcohol Dehydrogenase Catalyzed Oxidations of Diols Containing a Prochiral Center[1a,b]

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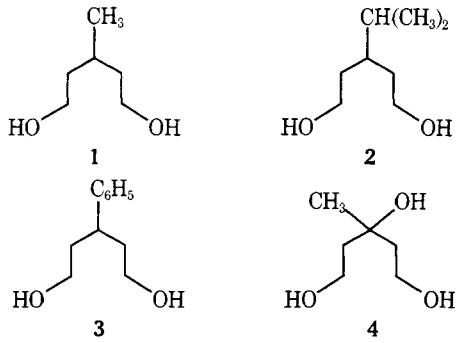
Abstract: The practicality of exploiting the enantiotopic specificity of horse liver alcohol dehydrogenase (HLADH) has been demonstrated using substituted pentane-1,5-diol substrates in which C-3 is a prochiral center. The catalysis was stereoselective for the pro-*S* hydroxyl group in each case. HLADH catalyzed oxidation of 3-methylpentane-1,5-diol gave (3*S*)-3-methylvalerolactone of >90% optical purity. The corresponding 3*S* lactones obtained with 3-isopropyl- and 3-phenylpentane-1,5-diols as substrates were of 25 and 21% optical purities, respectively. From the more highly C-3 substituted substrate, 3-hydroxy-3-methylpentane-1,5-diol, the product was (3*S*)-mevalonic lactone (14% optical purity). The methyl and isopropyl lactones were formed in situ by HLADH catalyzed oxidation of the cyclic hemiacetal form of the initial hydroxyaldehyde product. The 3-isopropyl and 3-hydroxy-3-methyl hemiacetals were poor HLADH substrates and were oxidized to their lactones chemically. When enzyme-catalyzed oxidation of the hemiacetal intermediate could occur, its stereospecificity influenced the optical yield to a significant degree. The stereospecificities of the oxidations, which are very sensitive to the nature of the C-3 substituent, are all interpretable in terms of a diamond lattice section of the enzyme's active site. All reactions were performed on a preparative (up to 2 g) scale and good (up to 75%) yields of hemiacetal or lactone products were isolated.

The ability to effect stereoselective transformations of enantiotopic groups attached to a prochiral center is an important aspect of asymmetric synthesis for which the current techniques are woefully inadequate.[2] The capacity of enzymes to distinguish such groups is well documented,[3-5] but their potential as practical catalysts for this purpose remains largely untapped.[5b] During the course of our overall evaluation of the synthetic utility of enzymes in this regard, we have initiated

an investigation of the enantiotopic specificity of horse liver alcohol dehydrogenase (HLADH[6]). HLADH is a commercially available NAD^+ dependent oxidoreductase capable of effecting regiospecific and stereospecific CH(OH) $\rightleftharpoons$ C=O transformations on a broad spectrum of substrates.[5b,7] Our interest in its potential for catalyzing the selective oxidation of enantiotopic hydroxyl groups was prompted by the report that HLADH mediated oxidation of glycerol proceeded with pro-*S* specificity to give L-glyceraldehyde exclusively.[8] The scope of this reaction has now been explored further using the pentane-1,5-diol substrates **1–4.** HLADH is found to exhibit

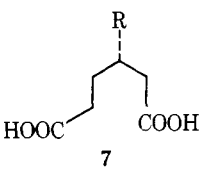


preparatively viable enantiotopic specificity towards this series of substrates, with the pro-*S* hydroxyl group being preferentially oxidized in each case. As in other recent[5b,7] demonstrations of the asymmetric synthetic utility of HLADH, the results are generally rationalizable in terms of the latest[5b,7] diamond lattice[9] section of the enzyme's active site.

Results

The starting diols **1–4** were all known compounds and were prepared by the literature methods or by unexceptional alternative routes. A routine assay showed them to be good substrates of the enzyme, with each being oxidized at a rate comparable to that of ethanol.[10] The preparative-scale HLADH catalyzed oxidations of **1–4** were carried out under the usual[5b,7] pH 9 reaction conditions using FMN recycling[11] of catalytic amounts of the expensive NAD^+ coenzyme.

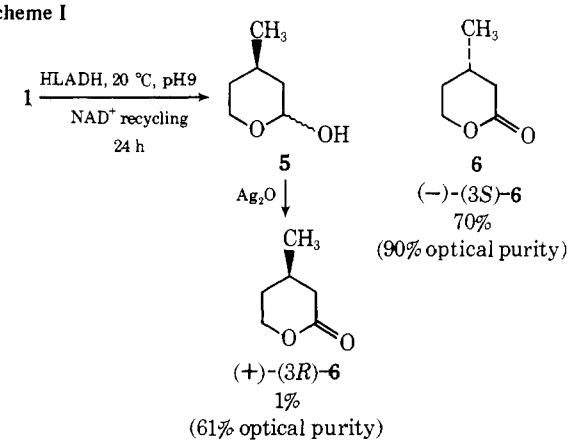
Enzyme-catalyzed oxidation of the 3-methyldiol **1** was terminated when GLC analysis showed it to be >95% complete. The results are summarized in Scheme I. The major product was virtually optically pure (−)-(3*S*)-3-methylvalerolactone (**6**). Traces of unreacted diol and of the hemiacetal **5** were also isolated. Oxidation of the latter with silver oxide gave (3*R*)-**6,** the enantiomer of the major product, of significant enantiomeric purity. The absolute configurations and optical purities of the enantiomers of **6** were determined by conversion of (−)-**6** into the previously characterized (−)-(3*S*)-3-methyladipic acid[12,13] (**7,** R = CH_3).



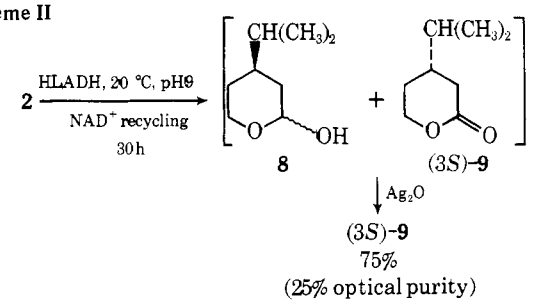
The oxidation of 3-isopropylpentane-1,5-diol (**2**) was almost complete in 30 h. The reaction mixture contained both the hemiacetal **8** and the lactone **9** together with a trace of unreacted diol **2.** The mixture of **8** and **9** was subjected to silver oxide oxidation to give the isopropyl lactone **9,** enantiomerically enriched in the 3*S* enantiomer, as shown in Scheme II. The configuration and optical purity of the lactone product **9** was established by its conversion[14] into (−)-(3*S*)-3-isopropyladipic acid (**7,** R = $CH(CH_3)_2$) and also by its transformation into (+)-(2*S*)-2-isopropylsuccinic acid (**10**).[15,16]

The Scheme II reaction was repeated several times using

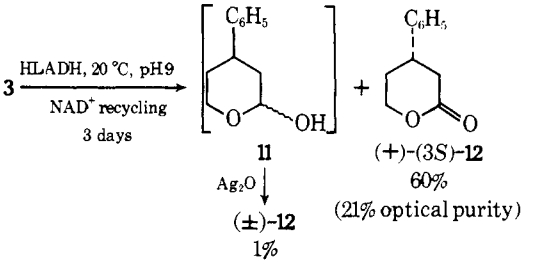
Scheme I



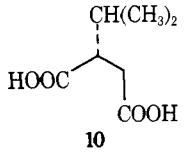
Scheme II



Scheme III

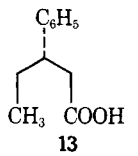


very slightly varied reaction periods in order to obtain a product mixture containing different proportions of hemiacetal **8** and



lactone **9.** The optical yields of the samples of lactone finally isolated were found to be very dependent on the ratio of **8:9.** Silver oxide oxidation of enzymically derived mixtures of **8** and **9** in the ratios of 59:41, 39:61, and 28:72 gave 3*S*-**9** of 8, 10, and 25% optical purity, respectively.

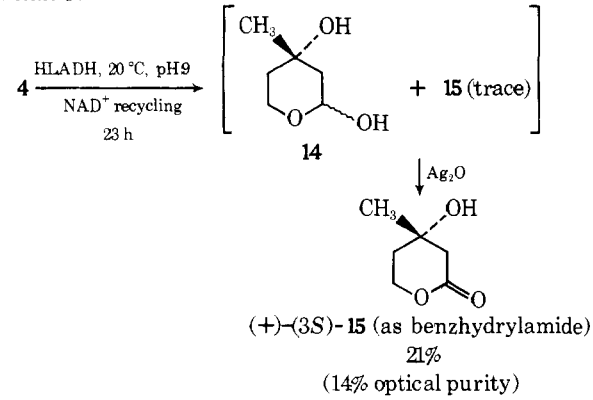
HLADH promoted oxidation of 3-phenylpentane-1,5-diol (**3**) was rather slow and the reaction was only ~70% complete after 3 days. The results obtained, with yields calculated on starting diol, are summarized in Scheme III. The absolute configuration and optical purity of the lactone (+)-**12** were determined by conversion into (+)-(3*S*)-3-phenylvaleric acid (**13**).[20,21] Surprisingly, the sample of **12** obtained on silver



oxide oxidation of the trace of hemiacetal **11** was found to be racemic.

The triol **4** was subjected to HLADH catalyzed oxidation

Scheme IV



for 23 h, after which time the reaction mixture contained (by GLC) the hemiacetal **14** (82%), mevalonic lactone (**15**, 4%), and residual **4** (7%). Silver oxide oxidation of the mixture of **14** and **15** gave mevalonic lactone (**15**), which was characterized as its benzhydrylamide.[22] The results are summarized in Scheme IV.

Discussion

All the enzyme-catalyzed oxidations were carried out on synthetically significant (up to 2 g) amounts of the diols **1–4.** Each oxidation was allowed to proceed to as close to completion as practicable, since enantiotopically selective transformations on substrates possessing a prochiral center are true asymmetric inductions. This obviates the often wasteful necessity of terminating enzyme-mediated transformations after ~50% of reaction with chiral or racemic substrates.

The absolute configurations and optical purities of the Scheme I–IV products were assigned using the most easily accessible of the previously characterized reference compounds in each case.[23] Care was taken to establish that no epimerization occurred during any of the correlation sequences. Also, the possibility of optical fractionation during recrystallization was guarded against by monitoring mother liquor rotations up to the >90% recovery point. Where the literature values for the rotation of a reference compound differed, the optical purity of the Scheme I–IV product concerned was always calculated conservatively. Thus, the optical purities cited for lactones **6** and **15** are minimum values.[24]

HLADH is seen to exhibit pro-*S* hydroxyethyl selectivity to a greater or lesser degree toward each of the diol substrates **1–4.** The stereospecificity of the overall process is almost total for the 3-methyldiol and then decreases monotonically as the C-3 position becomes progressively more hindered. While it is recognized that chiral centers with the same sequence rule descriptors need not be of the same configurational type, oxidation of the methyl, isopropyl, and phenyl substrates **1–3** does take place in the same configurational sense viz. with the C-3 hydrocarbon substituents becoming α oriented in the Scheme I–III representations of the lactone products. The oxidation of glycerol also takes place in the same configurational sense to give (2*S*)-glyceraldehyde as the only product.[8]

The pro-*S* hydroxyl group specificity of HLADH toward such aliphatic diol substrates thus seems to be virtually absolute when the substituent at the prochiral center is small, such as methyl or hydroxyl. In order to explore this aspect further, the stereospecificity of the enzyme towards the diol **4,** in which the orienting influences of the methyl and hydroxyl groups are opposed, was evaluated. The fact that any enantiotopic specificity would manifest itself in the formation of a chiral mevalonic lactone precursor was an additional stimulus. As Scheme IV shows, the 3*S* configuration resulting from "α orientation" of the hydroxyl group is marginally favored in this reaction. The ability of the hydroxyl group to offset the influence of methyl is attributed to steric, rather than polar, factors (see diamond lattice analysis below).

The hydroxyaldehydes formed initially presumably undergo subsequent enzyme-catalyzed oxidation in their hemiacetal form.[27] The rate of this reaction appears to be controlled by the nature of the C-3 substituent. For the 3-methyl substrate (Scheme I), oxidation of the hemiacetal **5** is evidently facile. However, the reaction becomes progressively slower as the C-3 position becomes more hindered. A significant proportion of the isopropyl hemiacetal **8** remains in the final Scheme II reaction mixture and the C-3 disubstituted lactol **14** (Scheme IV) is almost a nonsubstrate.

The fact that the intermediate hemiacetals **5, 8,** and **11** are chiral and can act as substrates in their own right interferes with our ability to establish to what degree the overall enantiomeric enrichments observed are attributable to enantiotopic specificity in the primary oxidation step. For the Scheme I reaction the pro-*S* specificity of the initial step is evidently extremely high. Furthermore, that the trace of residual hemiacetal **5** has the opposite C-3 configuration to, and is of lower optical purity than, the product lactone (3*S*)-**6** shows that both oxidation steps proceed with the same stereochemical preference. On the other hand, for the phenyl compounds, the enantiomeric excess of (3*S*)-**12** would seem to be due exclusively to enantiomeric discrimination during HLADH catalyzed oxidation of the hemiacetal, while for mevalonic lactone **15** the asymmetric synthesis occurs exclusively during the first enzyme-mediated step.

The degree to which both types of stereospecificity can influence the overall enantiomeric enrichment of the final product isolated is further illustrated by the isopropyl-substrate reactions of Scheme II. Although in this case the hemiacetal **8** and lactone **9** were not separated prior to chemical oxidation, changing the balance of **8:9** in the final reaction mixture from 59:41 to 28:72 raised the optical purity of the lactone product of silver oxide oxidation from 8 to 25%.[29]

Diamond Lattice Section Analysis

Analysis of the stereospecificities observed in diamond lattice[9] terms was performed using the model described previously.[5b,7a]

Enantiotopic Specificity in Diol Oxidation. The preferred orientations of diols such as **1–4** are depicted in Figure 1. For primary alcohols, oxidation involves removal of the pro-*R* hydrogen from the *e-Re* lattice direction.[5b] For the diols **1–4,** the hydroxyethyl group undergoing oxidation must be oriented as shown in Figure 1 in order to avoid placing any part of the substrate in a forbidden or undesirable lattice location.[5b] The remainder of the substrate then occupies the less-hindered right hand side of the lattice.[5b,7b] The enantiotopic selectivity of the enzymic oxidation now depends on the relative abilities of the lattice positions surrounding C-3 of the substrates to accommodate the various substituents attached to the prochiral center. Upward locations, such as I, J, and their equivalent positions, while not wholly forbidden, are less than ideal and will be avoided if possible.[30] The underneath region U is quite heavily forbidden and thus orientation of the smallest substituent (H) in this direction will be very desirable. Both of the remaining two lattice positions adjacent to C-3 are formally allowed locations[5b] and can accommodate larger groups. However, the rate data on the reduction of 3-alkylcyclohexanones[31] show one of them (the one occupied by R in Figure 1(a)) to have limited bulk tolerance. This is presumably due to the fact that large groups in this position impinge on the highly forbidden adjacent position A. On the other hand, the equivalent position on the left hand side (occupied by the pro-*R* hydroxyethyl group in Figure 1(a)) is known from studies on 4-alkylcyclohexanones[5b,31] to accept large substituents without

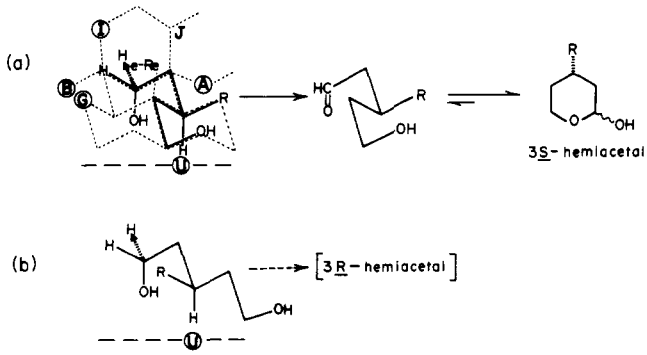


Figure 1. Diamond lattice analysis[5b,7a] of the enantiotopic specificity of HLADH toward diols **1–4.** The relevant portions of the lattice, including the forbidden or undesirable locations A, B, G, I, and U are indicated in dotted lines. The diol orientations shown are considered the most favorable, with the hydride equivalent being removed from the *e-Re* lattice direction and the bulk of the molecule occupying the less resistant to occupation right-hand side of the lattice. The situation shown in (a), which leads to the observed 3*S* hemiacetal products, avoids all unfavorable lattice locations. In contrast, formation of the 3*R* hemiacetal would require the relatively large CH_2CH_2OH group to be oriented adjacent to the highly forbidden A position, as represented in (b). The analysis is straightforward when the R group is small, as for **1** where R is methyl. For the diols **2** and **3** the distinctions in size between the R groups and the pro-*R* hydroxyethyl function become less marked and the enantiotopic stereoselectivity is reduced or lost. This is the result of the tendency of the isopropyl of phenyl groups to compete with the pro-*R* hydroxyethyl function for the unhindered location occupied by the latter in (a). For the diol **4,** with methyl and hydroxyl groups aspiring to the R position of (a), the stereoselectivity is in accord with the smaller of the two (hydroxyl) being marginally more favorably accommodated.

incurring significant rate penalties. Consequently, the position adjacent to A will be preferentially occupied by whichever of R or hydroxyethyl is the less sterically demanding.

Thus when R is much smaller than CH_2CH_2OH, the orientation depicted in Figure 1(a) leading to pro-*S* hydroxyethyl oxidation will be much favored over the one required for pro-*R* CH_2CH_2OH oxidation shown in Figure 1(b). The high pro-*S* enantiotopic specificity observed in the oxidation of **1,** where R = Me is in accord with this interpretation. The stereospecificity then decreases progressively for **2** and **3** as the size of the R group increases to isopropyl and phenyl, respectively. For **4,** the CH_3 and OH substituents are both small and compete with one another on almost equal terms for the preferred R location of Figure 1(a). Consequently, the minimal degree of asymmetric synthesis observed was not unexpected. The extent of pro-*S* specificity manifest (Scheme IV) indicates the marginal favoring of Figure 1(a)-like transition state with the least bulky[32] hydroxyl group adjacent to A. The very slow rate of oxidation of **4** is attributed to the fact that, in the absence of a hydrogen at the prochiral center, an unfavorable interaction of a sizable C-3 substituent with U cannot be avoided.

Stereospecificity in Hemiacetal Oxidation. Of each of the four stereoisomers of the hemiacetals **5, 8,** and **11,** only the 1*S*,3*S* compounds can be satisfactorily oriented without violating a forbidden position and with the hydroxyl group axial to permit removal of hydride from the required *e-Re* direction.[5b] This is shown in Figure 2. The 1*R*,3*S*, 1*R*,3*R*, and 1*S*,3*R* hemiacetals interact adversely with the U, G, and U regions, respectively, of the lattice. The observed 3*S* lactone preference is thus in accord with expectation. Again, the stereoselectivity is highest when the C-3 substituent is small, like methyl, and does not intrude into the forbidden domain of the A region. For each stereoisomer and chair conformer of the 3-hydroxy-3-methyl hemiacetal **14,** one of the C-3 methyl or hydroxyl substituents is directed towards the undesirable U region; HLADH catalyzed oxidation of **14** is thus negligibly slow.

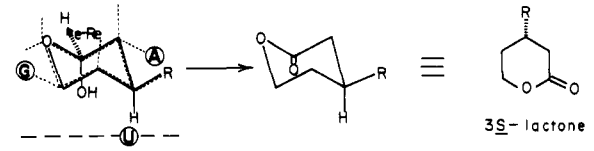


Figure 2. Diamond lattice analysis[5b,7a] of the stereospecificity of HLADH toward hemiacetals **5, 8, 11,** and **14.** For hemiacetals **5, 8,** and **11,** interactions with forbidden lattice positions are avoidable only in the transition state-like orientation shown for the 1*S*,3*S* stereoisomer. The conformation depicted meets the axial hydroxyl and *e-Re* hydride removal requirements[5b] of the analysis. The lattice thus predicts the preferential formation of the 3*S* lactone, as is observed in all cases. When R is small (Me) as in **5,** the process is quite stereospecific, but it becomes less so as the bulkier groups, such as the isopropyl and phenyl groups of **8** and **11,** respectively, intrude into the forbidden region surrounding A. The mevalonic lactone precursor **14** is virtually a nonsubstrate, owing to its inability to avoid interaction of either its C-3 methyl or hydroxyl substituent with U.

Experimental Section

Unless specified otherwise, sources of materials and details of general analytical procedures and equipment used are as described previously.[7] HLADH (EC 1.1.1.1) was assayed prior to use[33] and all amounts of enzyme quoted are in milligrams of active enzyme.

Preparation of Diols 1–4. 3-Methylpentane-1,5-diol (1). 3-Methylglutaric anhydride[34] (4 g, 31, 3 mmol) and $LiAlH_4$ (1.8 g, 47.3 mmol) were refluxed in dry tetrahydrofuran for 4 h. The solution was cooled, quenched with saturated aqueous NH_4Cl, and decanted from the residual sludge, which was washed with methylene chloride. The combined organic phases were dried ($MgSO_4$) and evaporated and the residual extracted into acetone. Evaporation of the acetone solution followed by distillation yielded **1** (2.6 g, 71% yield): bp 83–84 °C (0.1 Torr) [lit.[35] bp 139–146 °C (17 Torr)]; NMR (C^2HCl_3) δ 3.6–4.0 (6 H, S overlapping t, J = 6.6 Hz), 1.3–1.9 (5 H, m), and 0.9 (3 H, d, J = 5.9 Hz).

3-Isopropylpentane-1,5-diol (2). The 3-isopropylglutaric acid[36] starting material was prepared by the following improved route. *sec*-Butyraldehyde (72 g, 0.97 mol), ethyl cyanoacetate (113 g, 1 mol), and piperidine (1 ml) in benzene (200 ml) were refluxed under Dean–Stark conditions until dehydration was complete. The mixture was then evaporated and sodium dimethyl malonate (from dimethyl malonate (132 g, 1 mol) and sodium (2.6 g, 0.11 mol) in dry methanol (100 ml)) added. The mixture was refluxed for 4 h and was then cooled, acidified with 2 M aqueous HCl, and extracted several times with ether. The ether solution was washed with water, dried ($MgSO_4$), and evaporated to give an oil which was refluxed for 1 day with aqueous 48% HBr (350 ml). The solution was reduced in volume by 200 ml, an equivalent amount of aqueous 48% HBr added, and the solution refluxed for a further 1 day and then poured into cold water and extracted several times with ether. The ether phases were washed with water, dried ($MgSO_4$), and evaporated, and the oily product recrystallized from ethyl acetate/petroleum ether (30–60 °C) to give 3-isopropylglutaric acid (93.5 g, 54% yield): mp 100–101 °C [lit.[36] mp 102 °C]; NMR (C^2HCl_3) δ 2.4 (4 H, m), 1.8 (2 H, m), and 0.9 (6 H, d, J = 0.6 Hz).

The above diacid (93.5 g) and acetic anhydride (300 ml) were heated under reflux for 4 h to give 3-isopropylglutaric anhydride (74 g, 88% yield): bp 145–147 °C (0.1 Torr) [lit.[37] bp 171 °C (30 Torr)]; IR (film) 1802 and 1757 cm^{-1}; NMR (C^2HCl_3) δ 2.2–3.0 (4 H, m), 1.4–2.2 (2 H, m), and 0.95 (6 H, d, J = 6 Hz). 3-Isopropylglutaric anhydride (71 g, 0.46 mol) was reduced with sodium borohydride (17.3 g, 0.46 mol) in dry tetrahydrofuran (200 ml) according to the literature procedure.[38] 3-Isopropylvalerolactone (**9**) was obtained in 56% yield; bp 98–105 °C (0.1 Torr) [lit.[14] bp 138 °C (14 Torr)]; IR (film) 1742 cm^{-1}; NMR (C^2HCl_3) δ 4.3 (2 H, m), 2.2–2.8 (2 H, m), 1.3–2.0 (4 H, m), and 0.9 (6 H, d, J = 6.5 Hz).

The above lactone **9** (3 g, 21.5 mmol) and $LiAlH_4$ (0.8 g, 21.5 ml) in dry tetrahydrofuran (80 ml) was heated under reflux for 3 h. The cooled reaction mixture was then quenched with water, filtered, concentrated, and continuously extracted with ether for 12 h to give the isopropyldiol **2** (1.9 g, 62% yield): bp 96–98 °C (0.1 Torr) [lit.[36] bp 147–148 °C (15 Torr)]; NMR (C^2HCl_3) δ 3.7 (6 H, br s overlapping t, J = 6 Hz), 1.5–1.8 (6 H, m), and 0.9 (6 H, d, J = 6.5 Hz).

3-Phenylpentane-1,5-diol (3). 3-Phenylglutaric acid[39] (19.1 g, 0.09 mol) and $LiAlH_4$ (6.84 g, 0.18 mol) were refluxed in dry tetrahydrofuran (250 ml) for 4 h. Workup as for **2** gave, after fractional distillation, the phenyldiol **3** (7.5 g, 45% yield), bp 133–134 °C (0.1 Torr) [lit.[40] bp 145–146 °C (0.3 Torr)]; NMR (C^2HCl_3) δ 7.2 (5 H, m), 3.4 (4 H, t, J = 6.2 Hz), 2.7–3.2 (5 H, m overlapping br s), and 1.8 (4 H, m).

3-Methylpentane-1,3,5-triol (4). Of the four[41-44] potential literature approaches evaluated, $LiAlH_4$ reduction of mevalonic lactone[44] gave the best results. The methyl triol **4** (99.5% pure by GLC) was obtained in 84% yield: NMR (C^2HCl_3) δ 3.9 (7 H, s overlapping t, J = 7 Hz), 1.8 (4 H, m), and 1.3 (3 H, s). Its bis(3′,5′-dinitrobenzoate) derivative had mp 146–148 °C after recrystallization from benzene: NMR ($C^2H_3COC^2H_3$) δ 9.05 (6 H, m), 4.7 (4 H, t, J = 7.0 Hz), 2.15 (4 H, t, J = 7.0 Hz), and 1.4 (3 H, s). Anal. $C_{20}H_{18}N_4O_{13}$; C, H, N.

HLADH Catalyzed Oxidation of 3-Methylpentane-1,5-diol (1). The diol **1** (1.5 g, 12.7 mmol), NAD^+ (0.84 g, 1.27 mmol), and FMN[11] (11.2 g, 23 mmol) were dissolved in 0.05 M glycine–NaOH buffer (250 ml, pH 9). The pH of the resulting solution was adjusted to 9 with 5 M aqueous NaOH, HLADH (50 mg) added, and the solution kept at 20 °C for 23 h. The pH at that time (7.2) was readjusted to 9 and the reaction allowed to continue for a further 9 h. The pH was then raised to 12 with 5 M aqueous NaOH and the solution continuously extracted with chloroform for 2 days. The oil (164 mg) obtained contained unreacted diol (49%) and the hemiacetal **5** (29%). It was mixed with silver nitrate (0.5 g) in 50% aqueous ethanol (8 ml) and NaOH (0.25 g) in water (4 ml) added with stirring. The mixture was stirred overnight at 20 °C, filtered, and continuously extracted with chloroform for 2 days. This chloroform extract was discarded and the aqueous solution acidified to pH 3 with 12 M HCl and continuously extracted with chloroform for 1 day. After evaporation and molecular distillation of the latter extract, (+)-(3*R*)-3-methylvalerolactone (**6**, 14.3 mg) was obtained; it had $[\alpha]^{25}D$ +7.0 (*c* 0.14, $CHCl_3$) (61% optical purity, see below).

The aqueous solution from the original enzyme oxidation was acidified to pH 3 with 12 M HCl. Continuous chloroform extraction for 1 day followed by the above workup afforded (−)-(3*S*)-**6** (1.02 g, 70% yield): bp 93–94 °C (0.02 Torr) [lit.[45] (±) bp 110–111 °C (15 Torr)]; $[\alpha]^{27}D$ −24.8° (*c* 5.6, $CHCl_3$) (90% optical purity, see below); IR ($CHCl_3$) 1727 cm^{-1}; NMR (C^2HCl_3) δ 4.3 (2 H, m), 1.1–2.8 (5 H, m), and 1.05 (3 H, d, J = 5.6 Hz).

Absolute Configuration and Optical Purity Correlations of (−)-(3*S*)-6. A solution of (−)-(3*S*)-**6** (1.02 g, $[\alpha]^{27}D$ −24.8° ($CHCl_3$)) in ethanol (25 ml) was treated with excess dry HBr at 0 °C to give (−)-ethyl 5-bromo-(3*S*)-3-methylpentanoate (1.65 g, 82% yield): bp 88–89 °C (4 Torr) [lit.[46] (±) bp 105–107 °C (13 Torr)]; $[\alpha]^{25}D$ −12.1° (*c* 5.3, $CHCl_3$), IR ($CHCl_3$) 1724 cm^{-1}; NMR (C^2HCl_3) δ 4.15 (2 H, q, J = 7.3 Hz), 3.45 (2 H, t, J = 7.1 Hz), 1.7–2.4 (5 H, m), 1.25 (3 H, t, J = 7.3 Hz), and 1.05 (3 H, m).

Acetic acid (0.75 ml) and NaI (75 mg, 0.5 mmol) were added to KCN (0.435 g, 6.8 mmol) in water (0.3 ml).[14] The above (−)-ethyl 5-bromo-(3*S*)-methylpentanoate (0.65 g, 2.9 mmol) in ethanol (1.8 ml) was then added and the solution refluxed for 7 h. Workup, followed by one recrystallization from ethyl acetate–petroleum ether (30–60 °C), gave (−)-(3*S*)-3-methyladipic acid (**7**, R = CH_3, 350 mg, 75% yield): mp 89–90 °C (lit.[13] (+) mp 86–88 °C); $[\alpha]^{25}D$ −10.98° (*c* 3.2, $CHCl_3$), −8.2° (*c* 2, H_2O) [lit. (+) +11.5° (*c* 9.4 $CHCl_3$),[13] +9.3° (*c* 6.5, H_2O),[12] +7.5° (*c* 11, H_2O);[47] IR ($CHCl_3$) 3225–2565 and 1700 cm^{-1}; NMR (C^2HCl_3) δ 11.5 (2 H, s), 1.5–2.5 (7 H, m), and 1.0 (3 H, d, J = 5.8 Hz).

HLADH Catalyzed Oxidation of 3-Isopropylpentane-1,5-diol (2). The diol **2** (1.5 g, 10.3 mmol) was oxidized in the presence of HLADH (40 mg) as described above. After 30 h the pH was adjusted to 12 and the solution continuously extracted with chloroform for 24 h to give the hemiacetal **8** as a pale yellow oil (1.13 g). This was dissolved in 60% aqueous ethanol (70 ml) containing silver nitrate (10 g, 59 mol) and NaOH (4.8 g, 0.12 mol) in water (40 ml) added. The resulting suspension was stirred at 20 °C for 12 h and then worked up as described above for the **5** → **6** reaction. The 3-isopropylvalerolactone (740 mg) obtained was combined with that (523 mg) isolated by continuous chloroform extraction at pH 3 of the original aqueous enzymic reaction mixture. The combined lactone fractions were distilled to give (3*S*)-**9** (1.1 g, 75% yield): bp 61–62 °C (0.05 Torr) [lit.[14] (±) bp 138 °C (14 Torr)]; $[\alpha]^{25}D$ −6.3° (*c* 1.6, $CHCl_3$) (8% optical purity, see below); IR ($CHCl_3$) 1730 cm^{-1}; NMR (C^2HCl_3) δ 4.3 (2 H, m), 2.2–2.8 (2 H, m), 1.3–2.0 (4 H, m), and 0.9 (6 H, d, J = 6.5 Hz).

On repeating the above reaction for somewhat shorter time periods, **8**:**9** product ratios of 61:39 and 72:28 were obtained, which on silver oxide oxidation gave (3*S*)-**9** with $[\alpha]^{25}D$ −7.9° (*c* 3.2, $CHCl_3$, 10% optical purity) and −19.3° (*c* 0.8, $CHCl_3$, 25% optical purity), respectively.

Absolute Configuration and Optical Purity Correlations of (−)-(3*S*)-9. (a) **Via 7, R = $CH(CH_3)_2$.** (−)-(3*S*)-3-Isopropylvalerolactone (**9**, 0.39 g, $[\alpha]^{25}D$ −9.4° ($CHCl_3$)) was converted as described for (−)-(3*S*)-**6** to (+)-ethyl 5-bromo-(3*S*)-3-isopropylpentanoate (594 mg, 86% yield): bp 62–64 °C (0.02 Torr) [lit.[14] (±) bp 138 °C (14 Torr)]; $[\alpha]^{26}D$ +1.5° (*c* 5.5, $CHCl_3$); IR (film) 1733 cm^{-1}; NMR (C^2HCl_3) δ 4.14 (2 H, q, J = 7.2 Hz), 3.4 (2 H, t, J = 7.0 Hz), 2.2 (2 H, m), 1.6–2.0 (4 H, m), 1.15 (3 H, 5, J = 7.2 Hz), 0.95 and 0.96 (6 H, overlapping d, J = 6.7 Hz).

The above ethyl ester (590 mg) was then treated with potassium cyanide as for its 3*S* methyl analogue to give, after one recrystallization from water, (3*S*)-**7**, R = $CH(CH_3)_2$ (90 mg, 20% yield): mp 79–80 °C, (lit. (±) mp 85 °C,[14] (+) mp 71–73 °C[48]); $[\alpha]^{20}D$ −0.6° (*c* 0.9, Na^+ salt in H_2O) (lit.[49] $[\alpha]^{20}D$ +5.6° (Na^+ salt in H_2O)); NMR (C^2HCl_3) δ 11.8 (2 H, s), 2.0–2.5 (4 H, m), 1.4–1.9 (4 H, m), 0.9 and 0.92 (6 H, overlapping d, J = 6.4 Hz).

(b) **Via (3*S*)-10.** (+)-Ethyl 5-bromo-(3*S*)-3-isopropylpentanoate (1.67 g, $[\alpha]D$ +0.83° ($CHCl_3$)) obtained as above was refluxed in 2,4,6-trimethylpyridine (5 ml) for 2 h. The cooled solution was then poured into saturated aqueous $CuSO_4$ (100 ml) and extracted with ether. The evaporated ether extract was fractionally distilled to give (+)-ethyl 3-isopropyl-4-pentenoate (177 mg, 16% yield): bp 72–74 °C (10 Torr); $[\alpha]^{25}D$ +2.3° (*c* 1.8, $CHCl_3$); IR (film) 3060, 1733, and 1634 cm^{-1}; NMR (C^2HCl_3) δ 5.4–6.0 (1 H, m), 5.1 (1 H, m), 4.9 (1 H, m), 4.1 (2 H, q, J = 7.2 Hz), 2.2–2.5 (2 H, m), 1.6 (1 H, m), 1.2 (3 H, t, J = 7.2 Hz), 0.9 and 0.88 (6 H, overlapping d, J = 6.8 Hz). A spectroscopically identical sample of (±) ester prepared similarly had bp 48–50 °C (0.1 Torr). Anal. $C_{10}H_{18}O_2$; C, H.

Potassium hydroxide (0.4 g) in ethanol (10 ml) was added to the ethyl ester $[\alpha]^{25}D$ +2.3° ($CHCl_3$) (177 mg) in ethanol (5 ml). The solution was heated at 100° for 40 min, concentrated in vacuo, diluted with water (40 ml), acidified with 12 M HCl, and extracted several times with chloroform. The chloroform extracts were dried ($MgSO_4$) and evaporated and the crude acid dissolved in methylene chloride (10 ml) and ozonized at 0 °C. The blue color was purged with oxygen, the solution concentrated, and formic acid (3 ml) in 30% hydrogen peroxide (30 ml) added. The remaining methylene chloride was removed and the mixture heated at 100 °C for 1 h. After destroying excess peroxide with manganese dioxide, the solution was evaporated, with benzene being added to assist in azeotropic removal of water. The solid obtained was recrystallized from ethyl acetate–petroleum ether (30–60 °C) and then from benzene to give (3*S*)-**10** (46 mg): mp 112–113 °C [lit. mp (±) 118 °C;[50] (−) 94 °C[15]]; $[\alpha]^{25}D$ +2.0° (*c* 2.2, H_2O) [lit.[15] $[\alpha]^{20}D$ +22.99° (*c* 5.6, H_2O)].

HLADH Catalyzed Oxidation of 3-Phenylpentane-1,5-diol (3). The diol **3** (2.05 g, 11.4 mmol) was oxidized under the general conditions described for **1** using HLADH (35 mg). The reaction was allowed to proceed at 20 °C for 3 days with the pH being occasionally readjusted to 9 and with a further 15 mg of HLADH being added after 2 days. Continuous chloroform extraction at pH 12 yielded an oil (235 mg) containing (by GLC) unchanged **3** (70%) and the hemiacetal **11** (23%), which on oxidation with silver oxide gave racemic **12** (22 mg). Subsequent continuous extraction of the enzymic reaction solution at pH 3 afforded (3*S*)-**12** (1.2 g, 60% yield): bp 124–126 °C (0.07 Torr) [lit.[51] (±) bp 160–163 °C (1.2 Torr)]; $[\alpha]^{25}D$ +0.78° (*c* 5.3, $CHCl_3$) (21% optical purity, see below); IR ($CHCl_3$) 1730 cm^{-1}; NMR (C^2HCl_3) δ 7.3 (5 H, m), 4.3–4.5 (2 H, m), 2.5–3.2 (3 H, m), and 1.9–2.3 (2 H, m).

Absolute Configuration and Optical Purity Correlation of (+)-(3*S*)-12. The above sample of (3*S*)-**12** (1.2 g) was treated with HBr in ethanol[51] as described for (3*S*)-**6** to give (−)-ethyl 5-bromo-(3*S*)-3-phenylpentanoate (1.54 g, 79% yield): bp 103–105 °C (0.1 Torr) [lit.[51] 139–141 °C (0.6 Torr)]; $[\alpha]^{25}D$ −9.36° (*c* 5.0, $CHCl_3$); IR ($CHCl_3$) 1720 cm^{-1}; NMR (C^2HCl_3) δ 7.25 (5 H, m), 4.05 (2 H, q, J = 7.2 Hz), 2.9–3.6 (3 H, m), 2.6 (2 H, d, J = 7.5 Hz), 1.9–2.3 (2 H, m), and 1.05 (3 H, t, J = 7.2 Hz). This bromo ester (500 mg, 1.75 mmol) in benzene (20 ml) was reduced with stirring under nitrogen at 20 °C with tri-*n*-butylstannic hydride[52] (610 mg, 2.1 mmol) in

benzene (5 ml). After stirring for 20 h, the reaction mixture was refluxed for 4 h, evaporated, and the resulting oil heated at 100 °C for 2 h in 10% ethanolic KOH (60 ml). The cooled solution was then diluted with water (300 ml), acidified with 12 M HCl, and then extracted with ether (6 × 10 ml). The ether extract was decolorized with charcoal, dried, evaporated, and molecularly distilled to give (3*S*)-**13** as a crystallizing oil (240 mg, 78% yield): mp 54–58 °C (lit. (−) mp 35–41 °C,[20] (±) mp 60–61 °C[53]) $[\alpha]^{25}D$ +9.52° (*c* 2.4, C_6H_6), +3.59° (*c* 1.5, EtOH) [lit. +46.3° (C_6H_6),[21] +17.4° (EtOH, 81% optical purity)[20]]; IR ($CHCl_3$) 1706 cm^{-1}; NMR (C^2HCl_3) δ 11.4 (1 H, s), 7.2 (5 H, m), 2.5–3.2 (3 H, m), 1.3–1.8 (2 H, quintet with fine structure), and 0.7 (3 H, t, J = 7.2 Hz).

HLADH Catalyzed Oxidation of 3-Methylpentane-1,3,5-triol (4). The triol **4** (850 mg, 6.3 mmol) was oxidized at 20 °C under the usual conditions with HLADH (60 mg) as catalyst. After 23 h, the pH was adjusted to 4 and the solution continuously extracted with chloroform for 3 days to give an oil (630 mg) containing (by GLC) the hemiacetal **14** (82%) and mevalonic lactone (**15**, 4%). This oil was dissolved in water (10 ml) and added at 20 °C to a stirred suspension of silver oxide (prepared by the addition of NaOH (3.8 g, 95 mmol) in water (20 ml) to silver nitrate (8.2 g, 47 mmol) in water (10 ml)). After being stirred for 28 h at 20 °C, the mixture was continuously extracted with chloroform for 1 day and the chloroform extract discarded. The aqueous mixture was then acidified to pH 3 with 12 M HCl and continuously extracted with chloroform for 2 days to give an oil (378 mg) containing (by GLC) **15** (80%), which was characterized as its benzhydrylamide.[22] After two recrystallizations from ethyl acetate–petroleum ether (30–60 °C) a sample (404 mg, 56% yield from **15**, 21% yield from triol **4**) was obtained which had mp 94.5–95.5 ° C [lit. (−) mp 102–103 °C,[22] (±) mp 93–95 °C[54]); $[\alpha]^{25}D$ −0.50° (*c* 4.0, $CHCl_3$) [lit.[22] $[\alpha]D$ −2.7° ($CHCl_3$), 75% optical purity).

References and Notes

(1) (a) This work was supported by the National Research Council of Canada. (b) Abstracted from the Ph.D. Thesis of A. J. Irwin, University of Toronto (1975). (c) Ontario Graduate Fellow 1972–1973; National Research Council of Canada Scholar 1973–1975.
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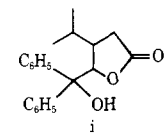
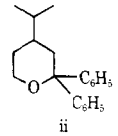


i



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(28) K. P. Lok, I. Goodwin, and J. B. Jones, unpublished results.
(29) A detailed study of the individual stereospecificities of HLADH catalyzed diol and cyclic hemiacetal oxidations of these types is now in progress.
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