was gently heated and stirred to produce an orange suspension and a yellow-orange precipitate. After 25 min the mixture was cooled to 25 °C and filtered to give 147 mg of nearly pure **1** (^{1}H NMR spectrum). This material was recrystallized from a mixture of 5 mL of $CHCl_3$ and 15 mL of EtOH to give 113 mg (54%) of pure **1** as an orange solid: mp 320–322 °C dec; ^{1}H NMR, δ 2.768 (s, $ArOCH_3$, 6 H), 3.000 (s, $ArOCH_3$, 3 H), 3.148 (2, $ArOCH_3$, 6 H), 7.167–7.563 (m, ArH, 15 H), 7.931 (d, ArH, 1 H, J = 8.8 Hz), 8.208 (s, ArH, 2 H), 8.538 (d of d, ArH, 1 H, J_o = 8.8 Hz, J_m = 2.3 Hz), 8.806 (d, ArH, 1 H, J = 2.3 Hz); mass spectrum, 818 (9), 817 (50), M^+ 816 (92), 802 (20), 785 (14), 784 (41), 755 (22), 754 (45), 741 (11), 740 (18), 643 (11) 639 (14), 638 (58), 637 (100). Anal. Calcd for $C_{47}H_{36}N_4O_{10}\cdot H_2O$: C, 67.62; H, 4.59. Found: C, 67.52; H, 4.48.

Determination of Binding Free Energies for Slowly Equilibrating Hosts. This procedure is illustrated as applied to phenol **5** and lithium picrate. A 0.00112 M solution of 3.48 mg (0.0056 mmol) of **5** in $CDCl_3$ was prepared in a 5.00-mL volumetric flask. A 1.00-mL aliquot was placed in a quartz tube fitted with a Teflon stopper and sleeve. A 1.00-mL aliquot of 0.000962 M lithium picrate in D_2O was added. The tube was stoppered, sealed with parafilm, and stirred at 25 °C with magnetic stirring. After 2 days, stirring was discontinued, the layers were allowed to separate, and 0.100-mL samples of each layer were diluted to 5.00 mL with acetonitrile with use of volumetric glassware. Absorbance readings were taken at 380 nm. Aliquots were taken at intervals until the absorbance readings remained constant. From the equilibrium–UV–absorbance values, the K_a and binding free energies were determined.[11] Table I reports the results.

Determinations of pK_a Values of Host 1 in the Presence of Potential Complexing Agents. The following procedures were representative. A yellow 4.45×10^{-5} M solution of **1** was prepared in a polypropylene volumetric flask with freshly distilled dioxane. An 0.800-mL portion of this solution gave an absorbance of 0.89 at 400 nm in a quartz UV cell. All additions were made directly into the UV cell with SMI micro/pettors. Solutions of more than 0.200 mL were added with disposable polypropylene cartridges. Solutions of less than 0.200 mL were added with disposable glass pipets which had been rinsed ten times with deionized water just prior to use to remove residual surface sodium. Solutions were added as quickly as possible with the glass pipets to minimize leaching of sodium ion from the glass. A 0.0100-mL portion of a 0.33 M aqueous solution of $NaClO_4$ was added to give a mixture of **1**·$NaClO_4$ and **1**$^-$·Na^+ with absorbances of 0.48 and 1.51 at 394 and 590 nm, respectively. Addition of 0.1800 mL of deionized water gave absorbances of 0.40 and 1.27 at 393 and 592 nm, respectively. Addition of 0.0100 mL of purified pyridine gave a blue solution of **1**$^-$·Na^+ with an absorbance of 1.51 at 592 nm.

A solution of 0.800 mL of **1** in dioxane, 0.0100 mL of an 0.33 M aqueous $NaClO_4$, and 0.1000 mL of deionized water was prepared to provide absorbances of 1.29 at 592 nm and 0.38 at 396 nm. Addition of two 0.0200-mL portions of a 1.2×10^{-3} M hydrochloric acid solution gave final absorbances of 0.95 at 590 nm and of 0.45 at 394 nm. The addition of 0.0300 mL of water gave absorbances of 0.93 at 592 nm and 0.43 at 395 nm. A 0.0100-mL portion of 1.2×10^{-3} M hydrochloric acid was added and gave absorbances of 0.71 at 590 nm and 0.49 at 396 nm. The microelectrode was inserted into the UV cell to give a reading of 4.59. Addition of 0.0100 mL of deionized water gave absorbances of 0.74 at 592 nm and 0.47 at 395 nm. An observed pH of 4.81 was recorded for this 80% dioxane–20% water (v/v) solution. A correction factor of 2.0 pK_a units for a solution with 3×10^{-3} M electrolyte in a 0.45 mol fraction of dioxane[20] was added to our pK_a observed value to give a corrected pK_a value of 6.81. The experiments involving **21**, **22**, DBN, K_2CO_3, $LiClO_4$, $CaCl_2$, and $MgCl_2$ were conducted with use of similar procedures and molar concentrations of salts and acids or bases. Each time the microelectrode was used it was calibrated with 4.05 and 7.00 aqueous buffers, or with 7.00 and 10.00 aqueous buffers, whichever was appropriate.

The pK_a values determined for **1**·$NaClO_4$ and **1**·$LiCl_4$ were shown to be rather insensitive to the exact amount of acid added as the equivalence point for [**1**·$MClO_4$] = [**1**$^-$·M^+] was approached. For example, when 75% of the acid had been added to reach the equivalence point for **1** complexing lithium, the corrected[20] pH of the medium was 6.0. When 112% of the acid needed had been added, the corrected[20] pH of the medium was 5.8. At the equivalence point, the pH was 5.9.

The pK_a values of the nonhost model compound **21** were determined with both NaOH and DBN as base by the above method in 80% dioxane–20% water (v/v). The pK_a value was 10.8 in each case. The pK_a values of **1**·$LiClO_4$ and **1**·$NaClO_4$ were estimated to be 8.0 and 8.1, respectively, in 89% dioxane–10% water–1% $(CH_3)_2SO$. That of **1** titrated with K_2CO_3 in 90% dioxane–10% water was estimated to be 14.0. The correction factors used with solvent systems of greater than 86% dioxane–water required extrapolation of reported values.[20]

Registry No. **1**, 111615-33-9; **1**$^-$, 111583-16-5; **1**$^-$·Li^+, 111583-20-1; **1**$^-$·Na^+, 111583-21-2; **1**·$NqClO_4$, 111583-28-9; **1**·$LiClO_4$, 111583-30-3; **2**, 72526-85-3; **3**·$LiFeCl_4$, 111583-23-4; **3**·LiCl, 111583-24-5; **3**·NaCl, 111583-25-6; **4**, 72526-87-5; **5**, 111583-17-6; **5**$^-$·Li^+, 111583-26-7; **6**, 111583-18-7; **7**, 111583-19-8; **16**, 89827-45-2; **20**, 83604-34-6; **21**, 33349-21-2; **22**, 100-02-7; Na^+, 17341-25-2; Li^+, 17341-24-1; K^+, 24203-36-9; Ca^{2+}, 14127-61-8; Mg^{2+}, 22537-22-0; lithium picrate, 18390-55-1; sodium picrate, 3324-58-1; dioxane, 123-91-1; DBN, 3001-72-7; 2,4-dinitrophenylhydrazine, 119-26-6.

Enzymes in Organic Synthesis. 38.[1] Preparations of Enantiomerically Pure Chiral Hydroxydecalones via Stereospecific Horse Liver Alcohol Dehydrogenase Catalyzed Reductions of Decalindiones[2,3]

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Contribution from the Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 1A1. *Received March 26, 1987*

Abstract: Preparative-scale horse liver alcohol dehydrogenase catalyzed reductions of symmetrical and racemic *cis*- and *trans*-decalindiones occur with concurrent regio- and stereospecificity to give good yields of enantiomerically pure keto alcohol products. In each case, the reduction occurs to give the (*S*)-chirality alcohol in a manner that is completely predicted by the cubic section active-site model. The chiral synthon utility of such keto alcohols is illustrated by a direct and efficient synthesis of (+)-(4*R*)-twistanone from *cis*-decalin-2,7-dione in 51% overall yield.

The broad spectrum of asymmetric synthetic opportunities provided by the use of enzymes as chiral catalysts is now well documented.[4] Horse liver alcohol dehydrogenase (HLADH[5]), a commercially available nicotinamide coenzyme dependent en-

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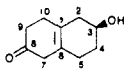
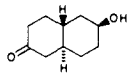
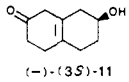
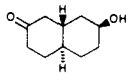
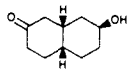
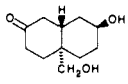
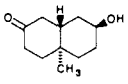
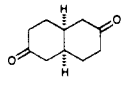
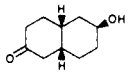
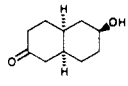
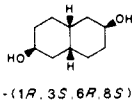
Table I. Results of HLADH-Catalyzed Reduction of Decalindiones **1–7**[a]

substrate	product	yield, %	de,[b] %	ee,[b] %
1[c]	 (−)-(3*S*)-**9**	34[d]	na[e]	>98
2	 (+)-(3*S*)-**10**	64	>98	>98
3[c]	 (−)-(3*S*)-**11**	18[d]	na[e]	>98
4	 (+)-(3*S*)-**12**	79	>98	>98
5	 (−)-(3*S*)-**13**	89	>98	>98
6	 (+)-(3*S*)-**14**	76	>98	>98
7	 (+)-(3*S*)-**15**	40	>98	>98

[a] Conditions: pH 6.5, 0.1 M phosphate buffer, 20 °C, NADH recycling. [b] Error limits ±2%. [c] pH 7.0. [d] After removal of isomerized α,β-unsaturated contaminant. [e] Not applicable.

Table II. Results of HLADH-Catalyzed Reductions of (±)-**8**[a]

substrate	redn, %	products	yield, %	de, %	ee,[b] %
(±)-**8**	50	 (−)-(1*S*,6*S*)-**8** +  (+)-(1*R*,3*S*,6*R*)-**16**	47 50	na[c] >98	>98 >98
(±)-**8**	65	(−)-(1*S*,6*S*)-**8** + (+)-**16** +  **17** +  (−)-(1*R*,3*S*,6*R*,8*S*)-**18**	33 27[d] 15[d] 17	na[c] >98[d] >98[d] >98	90 nd[e] nd[e] >98

[a] Conditions: pH 6.5, 0.1 M phosphate buffer, 20 °C, NADH recycling. [b] Error limits ±2%. [c] Not applicable. [d] Estimated from NMR. [e] Not determined.

zyme that catalyzes stereospecific C=O ⇌ CH(OH) interconversions of a wide structural range of ketone and alcohol substrates,[4,6] is one of the most versatile enzymes in this regard. The ability of enzymes to induce stereospecific transformations on symmetrical substrates is of particular asymmetric synthetic importance, and the value of HLADH in this respect has been clearly established in the oxidation mode, particularly with meso diol substrates.[6] The results reported in this paper demonstrate that useful chiral synthons can also be generated with equal facility by HLADH operating in its reduction direction on symmetrical dione substrates such as **1–7** and the racemate (±)-**8**.

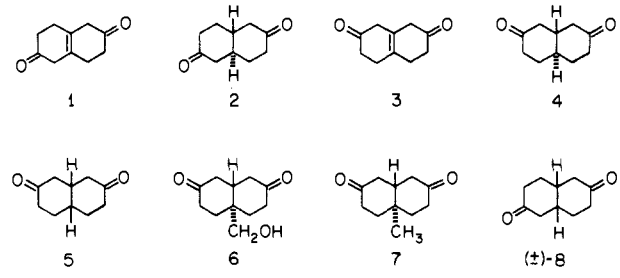


Table III. CD Spectra of Chiral Decalin Ketones

compound	concn[a], mM	θ^{25}, deg (λ, nm)	abs confign
(−)-**21**	48.8	0 (230), −4,483 (287), 0 (328)	1*R*,6*R*
(−)-**24d**	33.1	0 (230), −3,788 (287), 0 (330)	1*R*,6*R*
(−)-**8**	46.2	0 (230), +1,093 (287), 0 (325)	1*S*,6*S*
(+)-**8**	17.6	0 (235), −1,030 (287), 0 (328)	1*R*,6*R*
(+)-**10**	47.2	0 (225), +4.426 (287), 0 (322)	1*R*,3*S*,6*S*
(+)-**12**	36.1	0 (230), +5.317 (287), 0 (330)	1*S*,3*S*,6*S*
(−)-**13**	13.9	0 (240), +76.3 (287), 0 (330)	1*S*,3*S*,6*R*
(+)-**14**	55.3	0 (225), +3.228 (287), 0 (330)	1*S*,3*S*,6*R*
(+)-**15**	34.9	0 (230), +4.285 (287), 0 (330)	1*S*,3*S*,6*S*
(+)-**16**	33.7	0 (230), +180.8 (287), 0 (330)	1*R*,3*S*,6*R*

[a] In EtOH.

Results

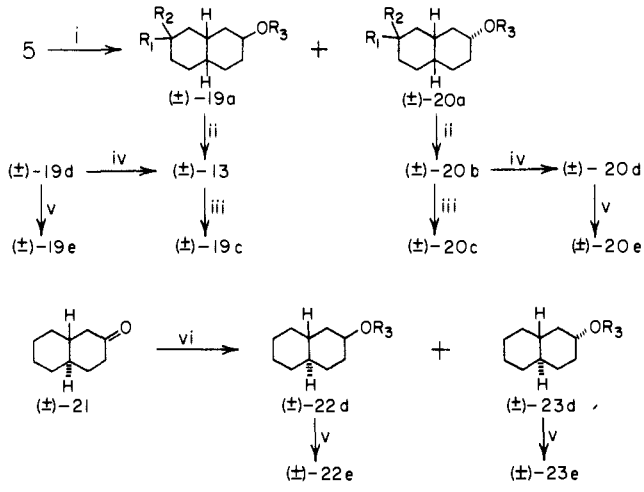
Substrates. The substrates evaluated were the decalindiones **1–8**. The preparations of these compounds, and their preliminary evaluations as viable substrates for preparative-scale HLADH-catalyzed reductions, have been described previously.[1]

Preparative-Scale HLADH-Catalyzed Reductions of 1–8. The decalindiones **1–8** were individually subjected to HLADH-catalyzed reduction on a 1–4-g scale with ethanol as the coupled substrate for recycling[7,8] the catalytic amounts of the nicotinamide coenzyme employed. The course of reaction was monitored by GLC. The products were isolated by extraction with chloroform followed by chromatography. The structures and relative configurations of the chiral centers of the hydroxy ketone products were established by comparison with the racemic reference structures described below. The results of the preparative-scale

(1) Part 37: Jones, J. B.; Dodds, D. R. *Can. J. Chem.*, in press.
(2) Abstracted from: Dodds, D. R. Ph.D. Thesis, University of Toronto, 1983. A preliminary communication on some of this work has been published.[3]
(3) Dodds, D. R.; Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1982**, 1080.

(4) (a) Suckling, C. J.; Wood, H. C. S. *Chem. Br.* **1979**, 2343. (b) Klibanov, A. M. *Science (Washington, D.C.)* **1983**, *219*, 722; *CHEMTECH* **1986**, 354. (c) Wong, C.-H.; Whitesides, G. M. *Aldrichimica Acta* **1984**, *16*, 27; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 617. (d) Battersby, A. R. *Chem. Br.* **1984**, 611. (e) Findeis, M. A.; Whitesides, G. M. *Annu. Rep. Med. Chem.* **1984**, *19*, 263. (f) Simon, H.; Bader, J.; Gunther, H.; Neumann, S.; Thams, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 539. (g) Jones, J. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1985; Vol. 5, pp 309–344. Jones, J. B. *Tetrahedron* **1986**, *42*, 3351.
(5) Abbreviations used: HLADH, horse liver alcohol dehydrogenase; NAD/H, oxidized and reduced forms, respectively, of nicotinamide adenine dinucleotide; de, diastereomeric excess; ee, enantiomeric excess; MTPA, (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl; Eu(fod)$_3$, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III); Eu(dcm)$_3$, tris-(di-(+)-campholylmethanato)europium(III).
(6) (a) Jakovac, I. J.; Goodbrand, H. B.; Lok, K. P.; Jones, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 4659. (b) Ng, G. S. Y.; Yuan, L.-C.; Jakovac, I. J.; Jones, J. B. *Tetrahedron* **1984**, *40*, 1235. (c) Bridges, A. J.; Sundararaman, P.; Ng, G. S. Y.; Jones, J. B. *J. Am. Chem. Soc.* **1984**, *106*, 1461. (d) Jones, J. B.; Francis, C. J. *Can. J. Chem.* **1984**, *42*, 2578. (e) Jones, J. B.; Jakovac, I. J. *Org. Synth.* **1985**, *62*, 10.
(7) Zagalak, B.; Frey, P. A.; Karabotsos, G. L.; Abeles, R. H. *J. Biol. Chem.* **1966**, *241*, 3028.
(8) Davies, J.; Jones, J. B. *J. Am. Chem. Soc.* **1979**, *101*, 5405.

Scheme I[a]



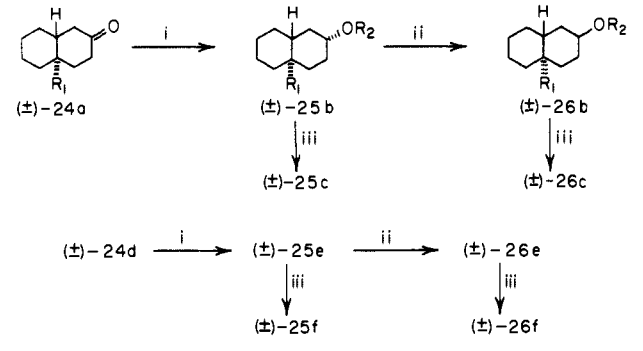
a, R_1 = OEt, R_2 = OEt, R_3 = H ; b, R_1R_2 = =O, R_3 = H

c, R_1R_2 = =O, R_3 = MTPA ; d, $R_1R_2R_3$ = H

e, R_1R_2 = H, R_3 = Me

[a] Conditions: (i) EtOH, H^+, CH(OEt); (ii) H_3O; (iii) MTPA-Cl; (iv) Wolff-Kishner; (v) NaH, CH_3I; (vi) $LiAlH_4$.

Scheme II[a]



a, R_1 = COOEt ; b, R_1 = CH_2OH, R_2 = H ; c, R_1 = CH_2OMe, R_2 = Me

d, R_1 = CH_3 ; e, R_1 = CH_3, R_2 = H ; f, R_1R_2 = Me

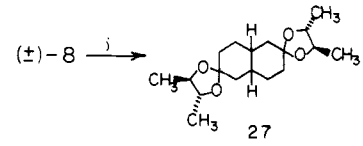
[a] Conditions: (i) $LiAlH_4$; (ii) ref 12 inversion; (iii) NaH, CH_3I.

HLADH-mediated reductions of the symmetrical diones **1–7** are summarized in Table I. In each case only one chiral hydroxy ketone was isolated,[9] with the balance of the material being the corresponding unreacted diketone substrate.

For the racemic dione **8**, termination of the reduction at the 50% stage yielded the hydroxy ketone (1*R*,2*S*,6*S*)-**16** and the unchanged (1*S*,6*S*) enantiomer of the starting ketone **8**. However, (1*S*,6*S*)-**8** was itself a poor substrate, and when the HLADH-catalyzed reduction was allowed to proceed further to the 65% of reaction stage, the products (1*S*,3*S*,6*S*)-**16** and (1*R*,3*S*,6*R*,8*S*)-**17** began to appear. The results are summarized in Table II.

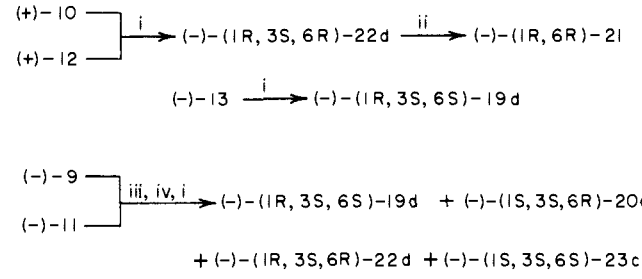
Diastereomeric and Enantiomeric Excess Determinations. An extensive survey of de and ee determination methods was carried out on the racemates of the chiral HLADH-derived products **8–18** of Tables I and II and of various racemic derivatives thereof.[10] The best analyses were found to be those based on ^1H NMR[11a] for the Table I compounds and on ^{13}C NMR[11b] for the Table II compounds. For the Table I analyses, the most suitable derivatives were the Mosher[11a] esters **19c** and **20c** and the decalin methyl ethers **19c**, **20e**, **22e**, **23e**, **25c**, **26c**, **25f**, and **26f**.

Scheme III[a]



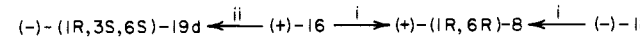
[a] Conditions: (i) H^+; (2*R*,3*R*)-butanediol.

Scheme IV[a]



[a] Conditions: (i) Wolff-Kishner; (ii) CrO_3; (iii) H^+; (iv) H_2, Pd/C.

Scheme V[a]



[a] Conditions: (i) CrO_3; (ii) Wolff-Kishner.

The racemates of these compounds required as reference standards were prepared as outlined in Schemes I and II. The base-line separations of the NMR resonances of the CF_3 or OCH_3 peaks of these compounds enabled the de's and ee's of the optically active Table III compounds derived from the HLADH-derived products **9–15**, obtained as described below in the configuration assignment section (via reaction with (MTPA)Cl for (−)-**13** and by Wolff-Kishner reduction followed by methyl ether formation for the rest), to be determined within ±2%.

The de and ee of the keto alcohol product **16** of reduction of the racemic diketone **8** were established on its methyl ether derivative **19e**. The ee of the recovered diketone (−)-**8** was determined by its conversion to the diketal **27**, as shown for (±)-**8** in Scheme III, and from the reference ^{13}C chemical shifts. The ee's of the keto alcohol (+)-**16** and the diol (−)-**18** followed in the same way from their oxidation to (+)-**8** with chromic acid and from their subsequent individual conversion to ketal **27** for NMR analysis. The results of these determinations are recorded in Table II.

Relative and Absolute Configuration Determinations. The C-3 configurations of the keto alcohol products **9–17** were established by comparison of their ^{13}C or ^1H NMR spectra, or those of their hydroxydecalin derivatives, with the reference standards of Schemes I and II of authenticated C-3 epimeric integrities. The ^{13}C NMR spectrum of the diol **18** showed five signals only, due to the presence of a center of symmetry, with the coincident C-3, C-8 signals at δ 66.4 indicating exo hydroxyl configuration.[13A] For those compounds with trans ring junctions, the C-3 configurations were further verified by ^{13}C or ^1H NMR assignments of the orientations of the hydroxyl substituents as axial or equatorial.[13]

The absolute configurations of (+)-**10** and of (+)-**12** and (−)-**13** were established by their reduction to the known[14] *trans*- and *cis*-**2** decalols **22d** and **19d**, respectively (Scheme IV). The unsaturated keto alcohols (−)-**9** and (−)-**11** possess only one chiral center. Its configuration in each was settled by reduction to a mixture of *cis*- and *trans*-2-decalols (−)-**19d**, (−)-**20d**, (−)-**22d**, and (−)-**23d**, as

(9) Except for **1** → **9** and **3** → **11**, where some isomerizations to the corresponding α,β-unsaturated ketones occurred during the reactions.

(10) These are described in detail in ref 2.

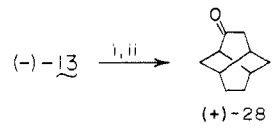
(11) (a) Dale, J.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Hiemstra, H.; Wynberg, H., *Tetrahedron Lett.* **1972**, 2001.

(12) Bose, A. K.; Lal, B.; Hoffman, W. A.; Manhas, M. S. *Tetrahedron Lett.* **1973**, 1619.

(13) (a) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic: New York, 1972; p 164. (b) Jackman, L. M. *Applications of NMR Spectroscopy in Organic Chemistry*; Pergamon: New York, 1959; p 116.

(14) Mislin, R. Ph.D. Thesis no. 4169, ETH, Zurich, 1968.

Scheme VI[a]



[a] Conditions: (i) $MeSO_2Cl$, pyr; (ii) NaH.

shown in Scheme IV. For all these decalol diastereomers, the sign of rotation unequivocally reflects the configuration of the hydroxyl-bearing center, with the (*S*)-chirality compounds all having negative rotations.[14] Only (3*S*) chirality in (-)-**9** and (-)-**11** can produce the (-)-rotating decalol mixtures observed, since the NMR comparisons above of their methyl ethers with their racemic counterparts (±)-**19e**, (±)-**20e**, (±)-**22e**, and (±)-**23e** established the single epimeric integrity of each C-3 center. By NMR, the proportions of **19d**/**20d**/**22c**/**23c** produced were 3:83:3:11 from (-)-**9** and 21:54:14:11 from (-)-**11**.

The absolute configurations in the HLADH-catalyzed reduction of (±)-**8** were ascertained as indicated in Scheme V. The stereochemistry of the keto alcohol product (+)-**16** was established by its reduction to (-)-**19d**, while oxidation gave diketone **8** of positive rotation, opposite to that of the recovered diketone (-)-**8**. Oxidation of the diol (-)-**18**, whose relative, exo, stereochemistry was determined above, also gave (+)-**8**, thereby settling its absolute geometry.

The two remaining outstanding absolute configurations, those of the C-6-substituted products (+)-**14** and (+)-**15**, were determined by circular dichroism using octant-rule analysis.[15] This established the absolute stereochemistries of the ring junctions, the relative geometry of the C-3 center having been determined above. The circular dichroism data for several other Table I and Table II ketones and for (-)-**21** and (-)-**24d** were also measured in order to provide further confirmation of the absolute configuration assignments. The results are recorded in Table III.

Synthesis of (+)-4-Twistanone (28). As an illustration of the chiral synthon utility of the enzyme-derived keto alcohol products of Tables I and II, (-)-**13** was converted in two steps[16] to (+)-4-twistanone (**28**) in 58% overall yield (Scheme VI). The racemic endo keto alcohol epimer of **13** was also converted to its mesylate and then treated with sodium hydride, but it did not cyclize to twistanone, thereby providing further confirmation of the exo C-3 stereochemistry of (-)-**13**.

Discussion

The diketone substrates **1**–**7** possess either rotational and/or reflective symmetry elements[1] and are therefore attractive candidates for conversion to chiral synthons via stereospecific enzyme-catalyzed transformations. The racemate **8** was included in the study because of its close structural similarity in **1**–**7**.

The preparative-scale HLADH-catalyzed reductions of **1**–**7** proceeded smoothly to give generally good yields of the keto alcohol products (Table I). Because the rates of reduction were somewhat slow, some reactions were not complete even after 8 days. In such cases, the isolated product yields were correspondingly reduced. Also, for the unsaturated dione substrates **1** and **3** and their keto alcohol products (+)-**9** and (-)-**11**, respectively, some isomerization to the α,β-unsaturated ketone materials occurred, even at pH 7, during the extended reaction periods. In all cases, recovery of unreacted substrate, or of isomerized unsaturated compounds, accounted completely for any outstanding material balance. Termination of the reduction of the racemic diketone **8** at the 50% point gave the product hydroxy ketone (+)-**16** and the recovered diketone (-)-**8** in enantiomerically pure forms. Under more forcing conditions, and permitting the reduction to proceed to the 65% of reaction point, the initial keto alcohol product (+)-**16** is partially reduced further to the diol (-)-**18**. Also, under these circumstances, the much preferred conversion of (-)-**8** to (+)-**16** is accompanied by some reduction of the less reactive dione enantiomer (+)-**8** to **17**,[17] as detected by ^{13}C NMR.

The NMR methodology described in the Results section enabled the diastereomeric integrities of the products **9**–**18** to be established unequivocally, since the spectra for each possible diastereomer of the racemic reference compounds (Schemes I and II) were distinctive. The questions of the C-3 hydroxyl orientation, exo or endo in the cis series or axial or equatorial in the trans series, were answered unambiguously by the same techniques. For the ee determinations, the methyl ether derivative approach failed only for the chiral *exo*-methoxydecalin [(-)-**19e**] derived from (-)-**13**. In this case, the ee determination had to be performed on the Mosher ester **19c** of (-)-**13**. The two methoxyl resonances of **25c** and **26c** were well separated and did not pose any interpretative or analytical problems. Of the solvents surveyed in the ee determination studies, viz. CCl_4, CS_2, $CDCl_3$, benzene-d_6, and toluene-d_8, the latter gave the best peak separations. No anomalies were discovered in the absolute configuration assignments.

Many applications of the chiral products of Tables I and II in asymmetric synthesis can be envisaged. The synthesis of (+)-twistanone shown in Scheme VI, which is the most direct route[19] to enantiomerically pure material, provides one such example. It also confirmed the absolute configuration assigned to (-)-**13** on the basis of its conversion to (-)-**19d**, for which some ambiguities existed in the reported[14,20] physical constants.

Cubic Active-Site Section Analysis of Stereospecificity. The stereospecificities of HLADH-catalyzed reductions of **1**–(±)-**8** are readily interpreted by use of the active-site section based on cubic space descriptors.[6a,18] The analysis for reduction of **4** is depicted in Figure 1. Four possible diastereomeric keto alcohol product structures can be written, each requiring a different active-site orientation of the substrate, as depicted in i–iv. However, the only favored enzyme–substrate binding orientation is the one shown in iv. This predicts the exclusive formation of (+)-**12**, in accord with the experimental results.

The cubic section analysis method described in Figure 1 for diketone **4** reduction is representative of the analyses for the other substrates **1**–**3** and **5**–(±)-**8**. In every case the favored stereochemical course of HLADH-catalyzed reduction predicted by cubic model analysis is in full accord with the experimental observation.[10] The stereochemical sense of reduction is clearly the same for all the structurally related diketones of this study, with (*S*)-chirality alcohols always produced, and with this enzyme-induced (*S*) center invariably adjacent to an (*R*)-chirality ring junction for the saturated substrates.

Experimental Section

Melting points (uncorrected) were determined in capillary tubes, and boiling points refer to Kugelrohr distillations. Unless specified otherwise, IR spectra were determined on KBr disks (for solids) and films (for liquids) on a Nicolet 5DX FTIR spectrophotometer, NMRs in $CDCl_3$ were determined on a Varian T60 or a CFT-20 for routine spectra, on a Varian XL200 for C-3 epimer configuration assignments, and on a Bruker WP80 for the shift reagent work. Mass spectra were measured on a Bell and Howell 21-490 instrument (low resolution) or on an AEI MS3074 (high resolution). Optical rotations and CD spectra were measured in EtOH (unless specified otherwise) on a Perkin-Elmer 141 polarimeter and a Jasco J-41A instrument, respectively. GLC analyses were done on a Varian 2700 (flame-ionization detection) with a CD S111 integrator. Elemental analyses were by Galbraith Laboratories. NAD^+ was purchased from Kyowa Hakko Kogyo and HLADH (EC 1.1.1.1) from Sigma, the activity being determined[23] prior to use.

(15) Moffitt, W.; Woodward, R. B.; Moscowitz, A.; Klyne, W.; Djerassi, C. *J. Am. Chem. Soc.* **1961**, *83*, 4013.
(16) Gauthier, J.; Deslongchamps, P. *Can. J. Chem.* **1969**, *45*, 297.
(17) The positively rotating mixture of (+)-**16** and **17** (2:1 ratio from ^{13}C NMR) isolated could not be separated. The absolute configuration shown for **17** in Table II is deduced from cubic active-site section analysis,[6a,18] as discussed later.
(18) Jones, J. B.; Jakovac, I. J. *Can. J. Chem.* **1982**, *60*, 19.
(19) Tichy, M. *Tetrahedron Lett.* **1972**, 2001.
(20) (a) Oritani, T.; Yamashita, K. *Agric. Biol. Chem.* **1974**, *38*, 1965. (b) Bec, J.-M.; Durand, J.; Huet, J. *Bull. Soc. Chim. Fr.* **1972**, 4344.
(21) The cubic section of ref 6a updates the limited regions originally formulated.[18] The most recent X-ray data[22] are in total accord with this active-site model.
(22) Horjales, E.; Branden, C.-I. *J. Biol. Chem.* **1985**, *260*, 15445.

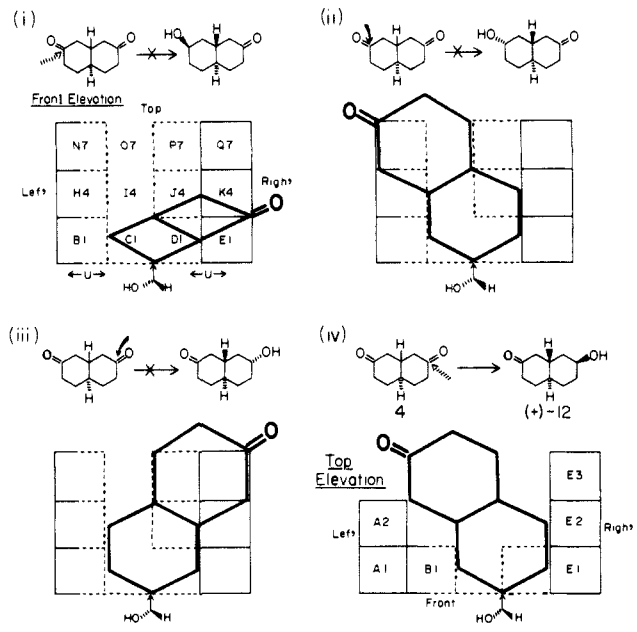


Figure 1. Cubic active-site section analysis of the substrate activity and product stereochemistry for the HLADH-catalyzed reduction of **4** to (+)-**12**. Each cube of the section is designated alphanumerically. In this figure, both front and top elevation perspectives[18] are used to depict the substrate orientations at the active site. The cubes bounded by solid lines are "forbidden" regions where substrate binding is precluded due to their being occupied by enzymic amino acid residues or by coenzyme. The spaces in front of, underneath, and above the defined cubic section are forbidden for the same reasons. Cubes bounded by broken lines are "limited" regions where substrate binding is possible, but not favored, as a result of their proximity to active-site amino acid residues.[21] The open areas are "allowed" space, where substrate can be readily accommodated. For reduction to occur, the C=O group must locate at the oxidoreduction site, identified by the arrow at the C1,D1 intersection. The substrate structures at the active site are shown in their alcohol-like forms, since this is considered to resemble the transition state of the reaction. The possible orientations of the substrate are then compared to identify the favored enzyme–substrate complexes i.e., those with all substrate groups in allowed regions. No reduction can take place if any part of the substrate occupies a forbidden region. If the substrate must locate in a limited region for reduction to occur, the rate is slowed markedly. The negative effects of limited-region binding are synergistic so that violation of two limited regions is equivalent to penetration of a forbidden cube. Full details of the model and its application are given in ref 18. For the dione **4** the active-site substrate orientations required for formation of each of the four different diastereomeric keto alcohol possibilities are shown in i–iv. The directions of hydride delivery that would be involved are indicated by the solid (top-face) or broken (bottom-face) arrows. (i) Reduction via this enzyme–substrate complex is precluded because the substrate would have to locate in forbidden regions E3,E4. (ii) Reduction cannot occur in this orientation because two limited regions, H4 and N8, are violated. (iii) This is excluded because of substrate penetration into forbidden regions K5 and Q8. (iv) Only in this enzyme–substrate complex leading to the observed product (+)-**12** is binding of the diketone **4** in wholly allowed regions possible.

Substrates. The diketone substrates **1**–(±)-**8** were prepared as described previously.[1]

Preparative-Scale HLADH-Catalyzed Reductions of Diketones 1–(±)-**8. General Procedure.** Each diketone (1 g) and NAD^+ (700 mg) were dissolved in 0.1 M phosphate buffer [400 mL, pH 6.5 (pH 7.0 for **1** and **3**)] containing EtOH (6 mL) at 25 °C to give a solution 12–15 mM in substrate, 2.6 mM in NAD^+, and 35 mM in EtOH. To this was added HLADH (150–300 units), and the mixtures was kept in the dark at 25 °C for 5–8 days, the progress of reaction being monitored by GLC. When the reaction was complete, or after 8-days maximum reaction time for the slowest substrate, the mixture was worked up by saturating with NaCl, extracting with $CHCl_3$ (4 × 50 mL), and rotoevaporation of the dried ($MgSO_4$) $CHCl_3$ solution. The crude product obtained was purified by chromatography on silica gel ($CHCl_3$/hexanes/MeOH, 80:19:1 elution) to give the pure hydroxy ketone product (and unreactive ketone enantiomer (−)-**8** and diol (−)-**18** for the reduction of (±)-**8**).

The individual reactions gave the following results, as summarized in Tables I and II.

Reduction of 1 (1 g) with HLADH (200 units) for 8 days (at pH 7) gave (3*S*)-hydroxybicyclo[3.3.0]dec-1(6)-en-8-one (**9**): 340 mg, 34% yield, >98% ee; mp (after recrystallization from Et_2O) 69.5 °C; $[\alpha]^{25}_D$ −68.5° (*c* 0.33); IR 1620, 1725, 3400 cm^{-1}; ^1H NMR δ 1.1–3.1 (13 H, envelope), 4.0 (1 H, br); ^{13}C NMR δ 27.56, 30.13, 38.14, 38.29, 43.56, 66.44, 125.1, 125.7, 211.1; mass spectrum, *m/e* calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0991.

Reduction of 2 (1 g) with HLADH (140 units) for 8 days gave (1*R*,3*S*,6*S*)-8-oxobicyclo[3.3.0]decan-3-ol (**10**): 640 mg, 64% yield, >98% ee; mp (after recrystallization from pentanes) 77–79 °C; $[\alpha]^{25}_D$ +24.5° (*c* 0.7); IR 1715, 3430 cm^{-1}; ^1H NMR δ 0.8–2.8 (15 H, envelope), 4.2 (1 H, br); ^{13}C NMR δ 27.48, 31.83, 33.21, 34.68, 38.80, 41.46, 42.84, 48.15, 65.88, 211.4; mass spectrum, *m/e* 168. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 8.59. Found: C, 71.57; H, 9.27%.

Reduction of 3 (1 g) with HLADH (300 units) for 8 days (at pH 7) yielded (3*S*)-hydroxybicyclo[3.3.0]dec-1(6)-en-9-one (**11**): 180 mg, 18% yield, >98% ee; bp 120 °C (0.25 mmHg); $[\alpha]^{25}_D$ −52.1° (*c* 0.27); IR 1715, 3400 cm^{-1}; ^1H NMR δ 1.6–3.4 (13 H, envelope), 4.0 (1 H, br); ^{13}C NMR δ 27.83, 30.00, 30.91, 38.49, 38.70, 44.12, 66.15, 123.1, 128.2, 211.0; mass spectrum, *m/e* calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0989.

Reduction of 4 (700 mg) with HLADH (150 units) for 8 days afforded (1*S*,3*S*,6*S*)-9-oxobicyclo[3.3.0]decan-3-ol (**12**): 554 mg, 79% yield, >98% ee; mp (after recrystallization from pentanes) 94–95 °C; $[\alpha]^{25}_D$ +31.9° (*c* 0.81); IR 1715, 3430 cm^{-1}; ^1H NMR δ 1.1–2.6 (15 H, envelope), 4.1 (1 H, br); ^{13}C NMR δ 18.32, 26.10, 32.50, 33.25, 36.63, 40.39, 41.44, 48.03, 65.42, 211.1; mass spectrum, *m/e* 168. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.33; H, 9.48.

Reduction of 5 (2 g) with HLADH (150 units) for 8 days gave (1*S*,3*S*,6*R*)-9-oxobicyclo[3.3.0]decan-3-ol (**13**): 1.78 g, 89% yield, >98% ee; mp (after recrystallization from hexanes) 65 °C; $[\alpha]^{25}_D$ −22.4° (*c* 0.8); IR 1715, 3420 cm^{-1}; ^1H NMR δ 1.2–2.5 (15 H, envelope), 3.9 (1 H, br); ^{13}C NMR δ 23.87, 28.40, 31.76, 33.90, 35.51, 36.95, 38.31, 44.36, 65.56, 212.1; mass spectrum, *m/e* 168. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.39; H, 9.46%.

Reduction of 6 (1 g) with HLADH (150 units) for 6 days yielded (1*S*,3*S*,6*R*)-6-(hydroxymethyl)-9-oxobicyclo[3.3.0]decan-3-ol (**14**): 400 mg, 40% yield, >98% ee; mp (after recrystallization from $CHCl_3$) 68–69 °C; $[\alpha]^{25}_D$ +26.6° (*c* 0.11); IR 1710, 3400 cm^{-1}; ^1H NMR δ 1.0–2.6 (13 H, envelope), 3.0–4.1 (5 H, br); ^{13}C NMR δ 27.57, 28.46, 34.35, 35.54, 36.94, 38.06, 43.93, 57.70, 65.39, 211.1. Elemental analysis performed on its derivative (−)-**35** is given below.

Reduction of 7 (1 g) with HLADH (170 units) for 6 days yielded (1*S*,3*S*,6*S*)-6-methyl-9-oxobicyclo[3.3.0]decan-3-ol (**15**): 760 mg, 76% yield, >98% ee; mp (after recrystallization from pentanes) 101–101.5 °C; $[\alpha]^{25}_D$ +28.4° (*c* 0.64); IR 1710, 3550 cm^{-1}; ^1H NMR δ 1.8 (3 H, s), 1.1–2.6 (14 H, envelope), 4.1 (1 H, quintet, *J* = 3 Hz); ^{13}C NMR δ 13.90, 28.46, 32.81, 33.79, 35.77, 37.14, 38.03, 40.49, 44.20, 65.27, 211.4; mass spectrum, *m/e* 182. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.50; H, 10.03.

Reduction of (±)-**8** (1 g) with HLADH (150 units) for 5 days (50% reduction) gave (1*R*,3*S*,6*R*)-8-oxobicyclo[3.3.0]decan-3-ol (**16**): 500 mg, 50% yield, >98% ee; bp 100 °C (0.07 mmHg) mp 63 °C; $[\alpha]^{25}_D$ +25.6° (*c* 0.52); IR 1715, 3430 cm^{-1}; ^1H NMR δ 1.0–2.7 (15 H, envelope), 3.9 (1 H, septet, *J* = 4 Hz); ^{13}C NMR δ 25.48, 27.95, 33.21, 33.53, 37.72, 37.88, 39.97, 45.32, 65.62, 211.9; mass spectrum, *m/e* 168. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.11; H, 9.61%.

Also recovered was the unchaned diketone enantiomer (1*S*,6*S*)-bicyclo[3.3.0]decane-3,8-dione (**8**): 470 mg, 47% yield, >98% ee; bp 90–100 °C (0.05 mmHg); mp 92–95 °C; $[\alpha]^{25}_D$ −23.0° (*c* 0.11); IR 1710 cm^{-1}; ^1H NMR δ 1.6–2.9 (envelope): ^{13}C NMR δ 27.92, 36.84, 39.24, 44.92, 210.2; mass spectrum, *m/e* 166. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.45; H, 8.62%.

On reduction for 8 days (65% reduction) (1*R*,3*S*,6*R*,8*S*)-bicyclo-[3.3.0]decane-3,8-diol (**18**) was isolated: 170 mg, 17% yield, >98% ee; bp 125 °C (0.15 mmHg) mp 176 °C; $[\alpha]^{25}_D$ −17.3° (*c* 0.58); IR 3400 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.0–2.1 (14 H, envelope including two overlapping quintets, *J* = 2 Hz at 2.0), 2.8 (1 H, br), 3.3 (1 H, br), 3.4–3.9 (2 H, m); ^{13}C NMR (THF + D_2O) δ 24.85, 34.63, 35.04, 38.77, 66.40; mass spectrum, *m/e* 170. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.29; H, 10.58%.

Relative Configuration, Diastereomeric Excess, and Enantiomeric Excess Determinations. Preparation of Racemic Reference Compounds. Exo- and Endo Keto Alcohols (±)-**13 and** (±)-**20b.** The method of Gauthier and Deslongchamps[16] was used to convert diketone **5** to *cis*-9,9-diethoxybicyclo[3.3.0]decan-3-one in 78% yield. This oxo ketal (10.0 g, 60 mmol) in dry THF (25 mL) was reduced with $LiAlH_4$ (1.5 g, 40

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mmol) in dry THF (75 mL) in the standard[24] way to give, after chromatography on silica gel (Et_2O/hexanes/MeOH, 50:49:1 elution), first *endo-cis*-9,9-diethoxybicyclo[3.3.0]decan-3-ol [(±)-**20a**]: 6.45 g, 65% yield; IR 1060, 1450, 3400 cm^{-1}; ^1H NMR δ 1.2–1.8 (20 H, envelope, t at 1.4, J = 6 Hz), 2.4 (1 H, br), 3.5 (1 H, br), 3.55 (4 H, dq, J = 6, 1 Hz); ^{13}C NMR δ 15.20, 15.27, 24.16, 26.94, 30.95, 32.51, 33.68, 34.96, 36.47, 37.30, 54.40, 54.79, 70.06, 99.67. Followed by *exo,cis*-9,9-diethoxybicyclo[3.3.0]decan-3-ol [(±)-**19a**]: 3.5 g, 35% yield; IR 1060, 1120, 1145, 3400 cm^{-1} (cf. ref 16 and 26); ^1H NMR δ 1.2–1.8 (20 H, envelope, t at 1.2, J = 6 Hz), 2.6 (1 H), 3.5 (1 H), 3.55 (4 H, dq, J = 6, 1 Hz); ^{13}C NMR δ 15.10, 15.29, 23.98, 26.98, 28.17, 32.62, 34.00, 34.13, 35.27, 39.95, 54.58, 65.98, 66.20, 100.4.

endo-(±)-**20a** (5.0 g, 20.7 mmol) in acetone (50 mL), water (50 mL), and 12 M hydrochloric acid (2 mL) was refluxed for 30 min and then cooled and extracted with Et_2O (5 × 75 mL). The dried ($MgSO_4$) ether solution was rotoevaporated to a viscous oil that was recrystallized from CH_3CN to give *endo-cis*-9-oxobicyclo[3.3.0]decan-3-ol [(±)-**20b**]: 2.5 g, 72% yield, mp 104 °C (lit.[20b] mp 92.5 °C); IR ($CHCl_3$) 1725, 3460 cm^{-1}; ^1H NMR δ 1.2–2.6 (5 H, envelope), 3.6 (1 H, br); ^{13}C NMR δ 26.06, 27.45, 29.30, 33.11, 35.96, 37.14, 40.16, 46.37, 69.68, 212.0.

exo-(±)-**19a** (2.4 g, 9.9 mmol) was hydrolyzed in the same way to give *exo-cis*-9-oxobicyclo[3.3.0]decan-3-ol [(±)-**13**]: 1.2 g, 72% yield; bp 110 °C (0.15 mmHg); IR 1055, 1710, 3420 cm^{-1} (lit.[25] 1050 cm^{-1}); ^1H and ^{13}C NMR as for (−)-**13** above.

Preparation of *exo*- and *endo-cis*-Decalols (±)-19d and (±)-20d. The endo keto alcohol (±)-**20b** (400 mg, 2.35 mol) in diethylene glycol (32 mL) containing KOH (450 mg, 3.2 equiv) and hydrazine hydrate (85% solution, 350 μL, 3.7 equiv) was heated at 120 °C for 2 h and then refluxed at 240 °C for an additional 4 h.[26] The reaction mixture was then cooled to 25 °C, poured into 2 N aqueous HCl solution (200 mL), and extracted with Et_2O (4 × 10 mL). The combined organic layers were dried ($MgSO_4$) and rotoevaporated to a white solid that was recrystallized from hexanes to give *endo-cis*-bicyclo[3.3.0]decan-3-ol [(±)-**20d**]: 305 mg, 85% yield; mp 103–104 °C (lit.[14,20a] mp 104 °C); IR 1050, 1445, 1460, 3280 cm^{-1}; ^1H NMR δ 1.2–1.8 (16 H, envelope), 2.4 (1 H, br), 3.6 (1 H, br); ^{13}C NMR δ 20.90, 25.73, 26.60, 29.89, 30.14, 30.26, 31.63, 34.59, 34.79, 35.29, 71.42.

exo-cis-(±)-**13** (225 mg, 1.32 mmol) was reduced by the same Wolff–Kishner procedure to give *exo-cis*-bicyclo[3.3.0]decan-3-ol [(±)-**19d**]: 150 mg, 60% yield; IR 1050, 1450, 3320 cm^{-1}; ^1H NMR δ 1.3–1.9 (17 H, envelope), 3.8 (1 H, br); ^{13}C NMR δ 19.34, 19.52, 22.20, 24.85, 25.69, 28.10, 29.96, 34.37, 35.45, 66.97.

Preparation of *trans*-Decalols (±)-22d and (±)-23d. *trans*-Bicyclo[3.3.0]decan-3-one[1,27] [*trans*-2-decalone [(±)-**21**]; 325 mg, 2.1 mmol] in dry THF (10 mL) was reduced[24] with $LiAlH_4$ (500 mg, 13.2 mmol) in dry THF (50 mL) to give a mixture of the axial hydroxy (±)-**22d** and equatorial hydroxy (±)-**23d** epimers as a clear oil (325 mg, quantitative yield) with largely coincident ^{13}C NMR signals: ^{13}C NMR δ 26.16, 26.41, 31.91, 32.72, 33.15, 33.69, 35.58, 36.27, 41.10, 42.22, 43.01, 66.59, 70.44. The axial *C*-OH signal at δ 66.59 and equatorial *C*-OH peak at δ 70.44 were diagnostic,[13a] and their intensities showed the ratio of (±)-**22d** to (±)-**23d** to be 14:86.

Preparation of (Hydroxymethyl)-*trans*-decalols (±)-25b and (+)-26b. *trans*-6-Carbethoxybicyclo[3.3.0]decan-3-one[1] [(±)-**24a**; 1.2 g, 5.4 mmol] in dry THF (50 mL) was reduced[24] with $LiAlH_4$ (1.0 g, 26.3 mmol) in dry THF (150 mL) at 25 °C to give *trans*-6-(hydroxymethyl)bicyclo[3.3.0]decan-3-ol [(±)-**25b**]: 860 mg, 95% yield; mp (after recrystallization from Et_2O) 142–143 °C; IR 1050, 1450, 3350 cm^{-1}; ^1H NMR δ 0.9–1.9 (17 H, envelope), 3.6–3.9 (3 H, br); ^{13}C NMR δ 21.47, 26.51, 28.26, 31.04, 33.19, 34.47, 37.84, 43.24, 58.56, 71.30 (equatorial *C*-OH); mass spectrum, m/e 184.

Hydroxyl inversion was effected by the general method of Bose et al.[12] The above equatorial alcohol (±)-**25b** (250 mg, 1.36 mmol) was dissolved at 25 °C in dry THF (20 mL) containing benzoic acid (335 mg, 2.75 mmol) and triphenylphosphine (720 mg, 2.75 mmol), and ethyl diazodicarboxylate (435 μL, 2.75 mmol) was then added. The reaction mixture was stirred at 25 °C for 18 h. The THF was removed by rotoevaporation, and the residual viscous oil was purified by chromatography on silica gel (Et_2O/hexanes, 1:4 elution) to give the decanol benzoate ester intermediate as a heavy oil: IR 1580, 1600, 1725 cm^{-1}.

The ester product was dissolved in a mixture of MeOH (50 mL) and saturated aqueous barium hydroxide solution (50 mL), and the resultant mixture was refluxed for 2 h. The hydrolysis mixture was cooled, diluted with saturated aqueous NaCl (200 mL), and extracted with CH_2Cl_2 (5 × 75 mL). The combined organic layers were dried ($MgSO_4$) and rotoevaporated to give a solid that was recrystallized from Et_2O to yield *trans*-6-(hydroxymethyl)bicyclo[3.3.0]decan-3β-ol [(±)-**26b**]: 160 mg, 80% overall yield; mp 118 °C; IR 1450, 3400 cm^{-1}; ^1H NMR δ 0.9–2.0 (17 H, envelope), 3.8 (2 H, br), 4.2 (1 H, quintet, J = 3 Hz, axial OH); ^{13}C NMR δ 18.50, 21.45, 22.68, 28.05, 28.51, 34.67, 35.44, 37.59, 37.89, 57.78, 66.54 (axial *C*-OH); mass spectrum, m/e 184.

Preparation of Methyl-*trans*-decalols (±)-25e and (±)-26e. *trans*-6-Methylbicyclo[3.3.0]decan-3-one [(±)-**24d**; 500 mg, 3.0 mmol] in dry THF (10 mL) was reduced[24] with $LiAlH_4$ (500 mg, 13.2 mmol) in dry THF at 25 °C to give *trans*-6-methylbicyclo[3.3.0]decan-3α-ol [(±)-**25e**]: 500 mg, quantitative yield; mp (after recrystallization from CH_3CN) 71 °C (lit.[28] mp 69–70 °C); IR 1040, 1060, 1450, 3350 cm^{-1}; ^1H NMR δ 0.8 (3 H, s), 1.0–1.5 (16 H, envelope), 2.1 (1 H, br), 3.6 (1 H, septet, J = 5 Hz, equatorial OH); ^{13}C NMR δ 15.67, 21.86, 26.69, 28.76, 31.32, 33.09, 38.24, 39.98, 41.15, 43.21, 71.38 (equatorial *C*-OH).

The inversion of the C-3 hydroxyl group of (±)-**25e** (335 mg, 2.0 mmol) was effected as described for **25b** → **26b** above to give *trans*-6-methylbicyclo[3.3.0]decan-3β-ol [(±)-**26e**]: 230 mg, 75% overall yield; bp 60 °C (0.3 mmHg); mp 88–89 °C, IR 1005, 1455, 3350 cm^{-1}; ^1H NMR δ 0.8 (3 H, s), 1.1–1.7 (16 H, envelope), 4.05 (1 H, quintet, J = 3 Hz, axial OH); ^{13}C NMR δ 14.58, 21.87, 26.99, 28.59, 28.85, 33.68, 35.46, 35.95, 37.90, 41.49, 66.96 (axial *C*-OH); mass spectrum, m/e 168.

Preparation of Decalin Methyl Ethers (±)-19e, (±)-20e, (±)-22e, (±)-23e, (±)-25c, (±)-26c, (±)-25f, and (±)-26f. The same general procedure was used for each. The decalol (0.5 mmol) was dissolved in dry THF (5 mL) and hexane-washed NaH (2 equiv, 4 equiv for **25b** and **26b**) added. The mixture was stirred for 30 min at 25 °C and CH_3I (3 equiv, 6 equiv for **25b** and **26b**) added. The mixture was stirred for 18 h at 25 °C, then poured into water (50 mL), and extracted with Et_2O (4 × 25 mL). The combined organic solution was dried ($MgSO_4$), filtered through alumina, and rotoevaporated carefully to give the methyl ether as a volatile oil that was purified by Kugelrohr distillation. The individual reactions gave the following results.

exo-3-Methoxybicyclo[3.3.0]decane [(±)-**19e**]: 79% yield from (±)-**19d**; bp 70 °C (0.25 mmHg); IR 1100, 1460, 1470 cm^{-1}; ^1H NMR (toluene-d_8) δ 0.9–2.0 (16 H, envelope), 3.0 (1 H, br), 3.17 (3 H, s); mass spectrum, m/e 168.

endo-3-Methoxybicyclo[3.3.0]decane [(±)-**20e**]: 87% yield from (±-**20d**; bp 70 °C (0.25 mmHg); IR 1100, 1375, 1450, 1470 cm^{-1}; ^1H NMR (toluene-d_8) δ 1.1–1.9 (16 H, envelope), 3.0 (1 H, br), 3.21 (3 H, s); mass spectrum, m/e 168.

trans-3β(a)- and 3α(e)-methoxybicyclo[3.3.0]decane [(±)-**22e** and (±)-**23e**]: 90% yield from (±)-**22d** and (±)-**23d**; bp 80–85 °C (0.2 mmHg); IR 1095, 1360, 1440 cm^{-1}; ^1H NMR (toluene-d_8) δ 0.5–2.0 (16 H, envelope), 2.9 (1 H, br), 3.11 (0.15 H, s, axial OCH_3), 3.18 (0.85 H, s, equatorial OCH_3); mass spectrum, m/e 168.

trans-3α(e)-Methoxy-6-(methoxymethyl)bicyclo[3.3.0]decane [(±)-**25c**]: 90% yield from (±)-**25b**; bp 90 °C (0.35 mmHg); IR 1110, 1120, 1450 cm^{-1}; ^1H NMR (toluene-d_8) δ 0.6–2.2 (15 H, envelope), 3.17 (3 H, s), 3.30 (3 H, s, equatorial OCH_3), 3.43 (2 H, s), 3.1–3.5 (1 H, br); mass spectrum, m/e 212.

trans-3β(a)-Methoxy-6-(methoxymethyl)bicyclo[3.3.0]decane [(±)-**26c**]: 92% yield from (±)-**26b**; bp 80 °C (0.3 mmHg); IR 1110, 1450 cm^{-1}; ^1H NMR (toluene-d_8) δ 0.7–2.0 (15 H, envelope), 3.12 (3 H, s), 3.16 (3 H, s, axial OCH_3), 3.398 (2 H, s), 3.2–3.4 (1 H, br).

trans-3α(e)-Methoxy-6-methylbicyclo[3.3.0]decane [(±)-**25f**]: 96% yield from (±)-**25e**; bp 60 °C (0.3 mmHg); IR 1110, 1125, 1180, 1450 cm^{-1}; ^1H NMR (toluene-d_8) δ 0.73 (3 H, s), 0.8–1.9 (15 H, envelope), 3.0 (1 H, br), 3.21 (3 H, s, equatorial OCH_3); mass spectrum, m/e 182.

trans-3β(a)-Methoxy-6-methylbicyclo[3.3.0]decane [(±)-**26f**]: 90% yield from (±)-**26e**; bp 60 °C (0.3 mmHg); IR 1105, 1125, 1370, 1450 cm^{-1}; ^1H NMR (toluene-d_8) δ 0.76 (3 H, s), 0.8–1.9 (15 H, envelope), 3.13 (3 H, s, axial OCH_3), 3.21 (1 H, quintet, J = 2 Hz); mass spectrum, m/e 182.

Preparation of (2*R*,3*R*)-Butanediol Diketal 27. Racemic *cis*-bicyclo[3.3.0]decane-3,8-dione [(±)-**8**; 100 mg, 0.6 mmol) in dry benzene (25 mL) containing (2*R*,3*R*)-butanediol (250 mg, 2.8 mmol) and *p*-TsOH (20 mg) was refluxed under Dean–Stark conditions for 3 h, then cooled, and poured into saturated aqueous K_2CO_3 (200 mL). The mixture was extracted with Et_2O (4 × 50 mL) and the ether solution dried ($MgSO_4$) and rotoevaporated to an oil, which on distillation yielded the *cis*-3,8-bis(2*R*,3*R*-butylenedioxy)bicyclo[3.3.0]decane (**27**): 165 mg, 90% yield; bp 120 °C (0.09 mmHg), mp 82 °C as a mixture of diastereomers; IR 1100, 1380, 1460 cm^{-1}; ^1H NMR δ 1.1–2.0 (26 H, envelope, s at 1.15 and 2.25), 3.6 (4 H, m); ^{13}C NMR in the supplementary material; mass

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spectrum, *m/e* 310. Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.94; H, 9.74. Found: C, 69.56; H, 9.75%.

Enantiomeric Excess Determinations. These were determined by ^1H NMR[11a] and ^{13}C NMR[11b] using the appropriate $\Delta\Delta\delta$ and δ values (see the supplementary material). The optically active derivatives of the chiral HLADH-derived products of Tables I and II required for these analyses were prepared by the same methods used for the corresponding conversions in the racemic series described above. In each case, unless recorded, the spectral properties of the optically active compounds were identical with those reported above for the corresponding racemates. The compounds prepared were as follows:

Mosher Ester. (−)-**13** was converted to its Mosher[11a] ester **19c** in 78% yield.

Methyl Ethers. Wolff–Kishner reductions were performed on the saturated Tables I and II keto alcohols and the hydroxydecalins obtained converted to their methyl ethers.

(−)-**10** gave (−)-**22d** and the methyl ether (−)-**22e**. (−)-**22d**: 90% yield; bp 60 °C (0.2 mmHg); mp 68–70 °C, $[\alpha]^{25}_D$ −8.3° (*c* 0.84) [lit.[14] mp 76 °C, $[\alpha]^{25}_D$ −8.0° (*c* 1.2, hexanes)]; mass spectrum, calcd for $C_{10}H_{18}O$ 154.1357, found 154.1350. (−)-**22e**: quantitative yield; bp 60 °C (0.2 mmHg); IR 1100, 1450 cm^{-1}; ^1H NMR (toluene-d_8) δ 0.6–2.0 (17 H, envelope), 3.11 (3 H, s), 3.30 (1 H, br).

(+)-**12** yielded (−)-**22d** [90% yield; $[\alpha]^{25}_D$ −9.35° (*c* 0.62)] and the methyl ether (−)-**22e** (quantitative yield).

(−)-**13** afforded (−)-**19d**: 95% yield; bp 60 °C (0.2 mmHg), $[\alpha]^{25}_D$ −10.9° (*c* 0.9, $CHCl_3$) [lit.[14] mp 39 °C (with a form having depressed mp[14,29]), $[\alpha]^{25}_D$ −15° (*c* 1.8, hexanes)]; mass spectrum, calcd for $C_{10}H_{18}O$ 154.1357, found 154.1348. (The de and ee determinations were performed directly on the Mosher ester of (−)-**13** above.)

(+)-**14** gave (−)-**26b**: 83% yield; mp ($CHCl_3$ recrystallization) 135–135.5 °C; $[\alpha]^{25}_D$ −8.7° (*c* 0.52). Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.49; H, 10.92%. Its dimethyl ether (−)-**26c** was obtained: 83% yield; bp 55 °C (0.1 mmHg).

(+)-**15** yielded (−)-**26e**: 95% yield; bp 80 °C (0.25 mmHg); mp 63–65 °C; $[\alpha]^{25}_D$ −6.6° (*c* 0.32). Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.52; H, 11.85. This gave the methyl ether (−)-**26f**: 95% yield; bp 60 °C (0.25 mmHg).

(+)-**16** yielded (−)-**19d**: 80%; yield; bp 60 °C (0.2 mmHg); $[\alpha]^{25}_D$ −11.3° (*c* 0.38). This was converted to the methyl ether (−)-**19e**: 76% yield; bp 60 °C (0.25 mmHg); IR 1100, 1450 cm^{-1}; ^1H NMR (toluene-d_8) δ 0.6–2.0 (17 H, envelope), 3.17 (3 H, s), 3.25 (1 H, br). This was used only for de analysis. It was not employed in ee analysis due to the absence of suitable $\Delta\Delta\delta$ values. Instead, the ketal **27** (below) method[11b] was employed.

Prior to methyl ether formation, the unsaturated hydroxy ketones (−)-**9** and (−)-**11** were hydrogenated. For each, 100 mg (0.6 mmol) in EtOH (25 mL) and 2 M aqueous HCl (4 mL) containing 5% Pd/C (50 mg) was shaken under H_2 (1 atm) for 18 h to give a mixture of saturated cis and trans keto alcohols. These were reduced by the above Wolff–Kishner method to give mixtures of the decalols (−)-**19d**, (−)-**20d**, (−)-**22d**, and (−)-**23d**. Their properties and those of their methyl ethers are detailed below.

Reduction of (−)-**9** gave the decalol mixture: 60% overall yield; bp 60–70 °C (0.2 mmHg); $[\alpha]^{25}_D$ −22.9° (*c* 1.1) [lit.[14] $[\alpha]^{25}_D$ (in hexanes) (−)-**19d** −15° (*c* 1.8), (−)-**20d** −32° (*c* 0.7), (−)-**22d** −8.0° (*c* 1.2), (−)-**23d** −0.6° (*c* 4.7)]; IR 3400 cm^{-1}; ^1H NMR δ 0.8–2.1 (17 H, envelope), 3.6 (1 H, br) mass spectrum, *m/e* 154. This was methylated to give (−)-**19e**, (−)-**20e**, (−)-**22e**, and (−)-**23e**: 3:83:3:11, 76% yield; bp 65 °C (0.25 mmHg); IR 1100, 1450 cm^{-1}; ^1H NMR (toluene-d_8) δ 0.8–2.0 (17 H, envelope), 3.0 (1 H, br), 3.1–3.2 (3 H total, 4 s).

Reduction of (−)-**11** yielded the decalol mixture: 50% overall yield; bp 65–70 °C (0.25 mmHg); $[\alpha]^{25}_D$ −22.6° (*c* 0.53). The mixture was methylated to give (−)-**19e**, (−)-**20e**, (−)-**22e**, and (−)-**23e**: (21:54:14:11, quantitative yield; bp 60 °C (0.2 mmHg); IR 1100, 1450 cm^{-1}; ^1H NMR (toluene-d_8) δ 0.8–2.0 (17 H, envelope), 3.0 (1 H, br), 3.1–3.2 (3 H total, 4 s).

(2*R*,3*R*)-Butanediol Diketals. The methodology used was as described for **27** in the racemic series. Unless reported otherwise, spectral data were as detailed for "(±)"-**27** above. The ^{13}C NMR spectra and assignments used in the ee determinations are contained in the supplementary material.

(−)-**8** gave the corresponding ketal **27**: 92% yield; bp 110 °C (0.25 mmHg); mp 94–96 °C.

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(−)-**18** was oxidized in acetone with Jones reagent to give (+)-**8**: 65% yield; $[\alpha]^{25}_D$ +44.7° (*c* 0.28). This was converted directly to its ketal **27**: 66% yield; mp 80–84 °C. (+)-**16** was converted to the same ketal in the same way.

Absolute Configuration Determinations. The absolute configurations of most of the Tables I and II compounds were determined during the ee analyses above. These correlations were as follows: (−)-(3*S*)-**9** and (−)-(3*S*)-**11** [to (−)-**19d**, (−)-**20d**, (−)-**22d**, and (−)-**23d**[14]], (+)-(1*R*,3*S*,6*R*)-**16** [to (−)-**19d**[14]], (−)-(1*S*,6*S*)-**8** and (+)-(1*R*,6*R*)-**8** [to (+)-**16**], and (−)-(1*R*,3*S*,6*R*,8*S*)-**18** [to (+)-**8**].

The absolute configurations of the remaining compounds [(+)-(1*S*,3*S*,6*S*)-**14** and (+)-(1*S*,3*S*,6*S*)-**15**] were determined by octant-rule[15] analysis of their CD spectra, which are recorded in Table III together with those of other HLADH-derived products of this study.

trans-Bicyclo[3.3.0]decan-3-one [*trans*-2-decalone [(−)-**21**]] was obtained in 74% yield by Jones oxidation of (−)-**22d** (from ee determination, Experimental Section): bp 60 °C (0.45 mmHg); $[\alpha]^{25}_D$ −39.5° (*c* 0.74) [lit.[14] $[\alpha]^{25}_D$ −52° (*c* 2.8, C_6H_6)].

trans-6-Methylbicyclo[3.3.0]decan-3-one [(−)-**24d**] was obtained in 85% yield by Jones oxidation of (−)-**26e** (from ee determination, Experimental Section): bp 80 °C (0.2 mmHg); $[\alpha]^{25}_D$ −29.0° (*c* 0.55).

Preparation of (+)-4-Twistanone (28). The basic method of Gauthier and Deslongchamps[16] was applied. (−)-*cis*-9-Oxobicyclo[3.3.0]decan-3-ol [(−)-**13**; 1.7 g, 10.2 mmol] was dissolved in dry pyridine (30 mL) and methanesulfonyl chloride (2.1 mL, 14.4 mmol) added, and the reaction mixture was stirred at 25 °C for 3 h. The mixture was then poured into 1% aqueous Na_2CO_3 (300 mL) and extracted with Et_2O (5 × 100 mL). The combined organic layers were washed with 2 M aqueous HCl until the washings were acidic, then dried ($MgSO_4$), and rotoevaporated to a solidifying yellow oil, which was recrystallized from Et_2O to give the desired mesylate: 2.0 g, 85% yield; mp 136 °C; $[\alpha]^{25}_D$ +5.02° (*c* 0.64, $CHCl_3$); IR 910, 1175, 1350, 1700 cm^{-1}; ^1H NMR δ 1.5–2.7 (14 H, envelope), 3.0 (3 H, s), 4.95 (1 H, *endo* proton[16]); ^{13}C NMR δ 23.92, 27.20, 27.95, 33.29, 33.45, 34.37, 38.41, 39.04, 44.79, 78.16, 210.7; mass spectrum, *m/e* 246. Anal. Calcd for $C_{11}H_{18}O_4S$: C, 53.64; H, 7.37; S, 13.02. Found: C, 53.60; H, 7.35; S, 12.91.

This exo mesylate (2.2 g, 8.9 mmol) was dissolved in dry 1,4-dioxane (100 mL) and NaH (1.2 g, 50% dispersion, washed with pentanes) added. The reaction mixture was refluxed for 4 h, cooled, and filtered through a fine sintered glass filter without quenching the NaH. The residue was washed carefully with Et_2O (3 × 25 mL), and the combined filtrate and washings were evaporated carefully to a yellow solid that was purified by chromatography on silica gel (Et_2O, hexanes, 1:4 elution) to yield a white solid material (910 mg, 68% yield). A sample of this material was further purified by preparative GLC (Carbowax 20M, 180 °C) to yield (+)-(4*R*)-twistanone (**28**): mp 172 °C (sealed tube), $[\alpha]^{25}_D$ +289° (*c* 0.116), identical with an authentic sample[19] [lit.[19] mp 172 °C, $[\alpha]^{25}_D$ +289° (*c* 0.2)]; IR 1205, 1730 cm^{-1}; ^{13}C NMR δ 13.20, 22.84, 24.41, 27.06, 30.03, 31.69, 43.01, 64.66, 217.2; mass spectrum, *m/e* calcd for $C_{10}H_{14}O$ 150.1050, found 150.1044.

Mesylation of (±)-Endo Keto Alcohol 20b. *cis-endo*-9-Oxobicyclo-[3.3.0]decan-3-ol [(±)-**20b**, 150 mg, 0.9 mmol] was converted by the above method to its mesylate: 155 mg, 70% yield; mp (from Et_2O) 79.5 °C; IR 1175, 1350, 1710 cm^{-1}; ^1H NMR δ 1.5–2.6 (15 H, envelope), 2.99 (3 H, s), 4.65 (1 H, br); ^{13}C NMR δ 26.47, 27.20, 27.58, 33.05, 33.61, 37.31, 38.86, 40.25, 46.13, 80.40, 210.6; mass spectrum, *m/e* 246. Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.64; H, 7.37; S, 13.02. Found: C, 53.52; H, 7.33; S, 13.26. On treatment with NaH, this did not cyclize to twistanone.

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Supplementary Material Available: Tables of ^{13}C NMR spectral assignments for **27** and for decalin Mosher ester and methyl ester reference compounds (2 pages). Ordering information is given on any current masthead page.