Enzymes in Organic Synthesis. 25.[1] Heterocyclic Ketones as Substrates of Horse Liver Alcohol Dehydrogenase. Highly Stereoselective Reductions of 2-Substituted Tetrahydropyran-4-ones

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Abstract: Horse liver alcohol dehydrogenase (HLADH) has been found to be an efficient catalyst for the reduction of O-heterocyclic ketones. Preparative-scale HLADH-catalyzed reductions of 2-substituted tetrahydropyran-4-ones are enantioselective, with reduction of each ketone enantiomer occurring to give cis or trans alcohol products of *S* configuration at the C-4 (alcohol) center. The major products of the reductions are the *trans*-tetrahydropyran-4-ols, all of which are of 100% enantiomeric excess. The cis alcohols are produced in very minor amounts only. The stereospecificities of the reductions are all interpretable in terms of the cubic-space section model of the enzyme's active-site region. The results extend further the already broad asymmetric synthetic potential of the enzyme.

Enzymes are becoming increasingly widely recognized as practical catalysts for asymmetric synthesis, and numerous illustrations of their applicability to a broad spectrum of synthetic problems have now been documented.[2] The synthetic utility of horse liver alcohol dehydrogenase (HLADH[3]), a nicotinamide coenzyme-dependent enzyme that catalyzes C=O ⇌ CH(OH) interconversions, has been particularly widely investigated.[2a-d,4,5] HLADH is a versatile oxidoreductase that accepts a wide structural range of aldehyde, ketone, and alcohol substrates and that exhibits well-defined and predictable[2d,4a] stereospecificity in almost all of the reactions it catalyzes.

Up till now, the majority of HLADH-catalyzed transformations reported have been of carbocyclic compounds. Little attention has been devoted to substrates containing heteroatoms.[4b,c,5] Accordingly, in view of the current asymmetric synthetic interest in chiral heterocyclic compounds,[6] we initiated[4b] a survey of the structural specificity and stereospecificity of HLADH toward heterocyclic ketones and alcohols. This survey has now been extended to oxygen heterocycles. In this paper details of the highly stereoselective preparative-scale HLADH-catalyzed reductions of the 2-substituted tetrahydropyran-4-ones (±)-**3a-d** to the corresponding cis and trans alcohols **1a-d** and **2a-d** are reported.

Scheme I

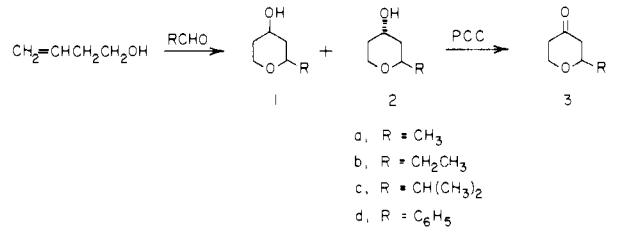

Table I. Relative Rates[a] of HLADH-Catalyzed Reductions of (±)-3a-d

substrate	rel rate
cyclohexanone	100
tetrahydropyran-4-one	14
(±)-3a	11
(±)-3b	16
(±)-3c	24
(±)-3d	148

[a] Rates of reduction were measured spectrophotometrically at 24 °C in 0.1 M phosphate buffer (pH 7).

Results

Preparation of Ketone Substrates and Their Racemic Alcohol Products. The racemic substrates **3a-d** were prepared by the general procedure of Hanschke[7] as outlined in Scheme I by oxidation of the mixture of cis- and trans-alcohols (±)-**1a-d** and (±)-**2a-d** obtained by condensation of the appropriate aldehyde with 3-butenol. The cis alcohols predominated in each mixture, to the extent of ~95% for **1a-c** and **2a-c** and ~80% for **1d** and **2d**. The cis and trans isomers were separable by column chromatography on silica gel (hexane–ether elution), but only for the 2-phenyl mixture **1d** and **2d** was the level of the trans compound high enough to provide the quantities needed. For the 2-alkyl derivatives **1a-c** and **2a-c**, the individual cis and trans isomers were separated by column chromatography from the cis–trans (~20:1) mixtures of alcohols obtained by reduction of the corresponding ketones (±)-**3a-c**.

The coincidence of C-2 and C-6 and of the diagnostically critical C-4 protons in the ^{1}H NMR spectra of the cis and trans components of each pair of 2-substituted tetrahydropyranols precluded direct identifications of the C-4 geometries[8] of the individual isomers. However, in each case the cis and trans configurations

(1) Part 24: Jones, J. B.; Jakovac, I. J.; Goodbrand, H. B.; Lok, K. P. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) (a) Jones, J. B.; Beck, J. F. *Tech. Chem. (N.Y.)* **1976**, *10*, 107. (b) Jones, J. B. In "Enzymic and Nonenzymic Catalysis"; Dunnill, P., Wiseman, A., Blakeborough, N., Eds.; Ellis Horwood/Wiley: Chichester/New York, 1980; pp 54-83. (c) Suckling, C. J.; Suckling, K. E. *Chem. Soc. Rev.* **1974**, *3*, 387. (d) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Suzuki, T.; Iwasaki, M.; Sasaki, Y.; Fujii, T. *J. Org. Chem.* **1981**, *46*, 2726. (e) Mosbach, K., Ed. *Methods Enzymol.* **1977**, *44*, 717-856. (f) Martinek, K.; Berezin, I. V.; *J. Solid-Phase Biochem.* **1978**, *2*, 343. (g) Chibata, I.; Tosa, T. *Annu. Rev. Biophys. Bioeng.* **1981**, *10*, 197. (h) Abbott, B. J. *Dev. Ind. Microbiol.* **1979**, *20*, 345. (i) May, S. W. *Enz. Microb. Technol.* **1979**, *1*, 15.

(3) Abbreviations used: HLADH, horse liver alcohol dehydrogenase; NAD^+ and NADH, oxidized and reduced forms, respectively, of nicotinamide adenine dinucleotide; MTPA, (+)-(2*R*)-α-methoxy-α-(trifluoromethyl)-α-phenyl acetate; $Eu(fod)_3$, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III).

(4) (a) Jones, J. B.; Jakovac, I. J. *Can. J. Chem.* **1982**, *60*, 19. (b) Davies, J.; Jones, J. B. *J. Am. Chem. Soc.* **1979**, *101*, 5405. (c) Jones, J. B.; Schwartz, H. M. *Can. J. Chem.* **1981**, *59*, 1574. (d) Jones, J. B.; Lok, K. P. *Ibid.* **1979**, *57*, 1025.

(5) (a) Van Luppen, J. J.; LePoivre, J. A.; Van Osselaer, T. A.; Lemiere, G. L.; Alderweireldt, F. C. *Bull. Soc. Chim. Belg.* **1979**, *88*, 829. (b) Hinson, J. A.; Neal, R. A. *J. Biol. Chem.* **1972**, *247*, 7106. *Biochim. Biophys. Acta* **1975**, *384*, 1. (c) Fries, R. W.; Bohlken, D. P.; Plapp, B. V. *J. Med. Chem.* **1979**, *22*, 356.

(6) (a) Scott, J. W.; Valentine, D. *Synthesis* **1978**, 329. (b) ApSimon, J. W.; Geguin, R. P. *Tetrahedron* **1979**, *35*, 2797. (c) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175. (d) Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375. (e) Hanessian, S. *Ibid.* **1979**, *12*, 159.

(7) Hanschke, E. *Chem. Ber.* **1955**, *88*, 1053.

(8) Wigfield, D. C.; Feiner, S. *Can. J. Chem.* **1978**, *56*, 789.

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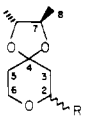
Table II. Chemical Shift Differences in the ^{13}C NMR Spectra of the Diastereomeric Ketals (±)-**4a–d**[a]

ketal structure	compd	Δδ, ppm C-2	C-3	C-4	C-5	C-6	C-7	C-8	other C
	**4a**	0.29	0.97	0	1.07[b]	0.21	0.37	0	0.13 (CH_3)
	4b	0.35	0.99	0	1.08[b]	0.24	0.27	0.12	0 (CH_2CH_3)
									0.07 (CH_2CH_3)
	4c	0.42	1.01	0	1.07[b]	0.26[b]	0.29[b]	0.13	0 ($CH(CH_3)_2$)
									0 ($CH(CH_3)_2$)
4	4d	0.34	1.02[b]	0	1.03	0.21	0.35	0	0 (C_6H_5)

[a] ^1H noise-decoupled spectra determined in C^2HCl_3. [b] Used for determining ee values shown in Scheme II.

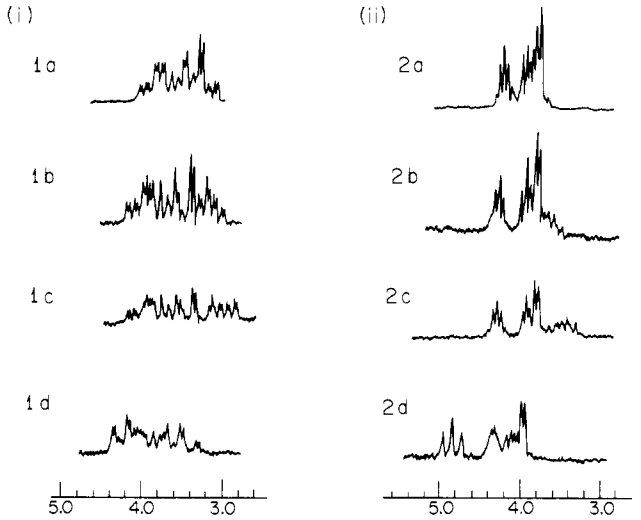


Figure 1. Characteristic ^1H NMR spectra of cis and trans alcohols **1a–d** and **2a–d**, respectively, in the 3–5-ppm (60 MHz) region: (i) cis isomers; (ii) trans isomers.

were unambiguously assigned by comparison of their distinctive ^1H NMR splitting patterns in the 3–5-ppm region (Figure 1) and by using the fully documented[8] cis- and trans-methyl derivatives **1a** and **2a** as reference standards.

HLADH-Catalyzed Reductions of (±)-3a–d. The rates of HLADH-catalyzed reductions of tetrahydropyranones relative to the rate of the standard reference substrate cyclohexanone under the same conditions are summarized in Table I. The unsubstituted parent, tetrahydropyran-4-one, and each of **3a–d** are seen to be satisfactory substrates of the enzyme, with rates of reduction well above the minimum required for preparative-scale reactions to be viable.[2a] In fact, the 2-phenyl derivative is reduced at an unprecedentedly high rate for a six-membered-ring ketone.

The racemic ketones **3a–d** were individually subjected to HLADH-catalyzed reduction on a 2-g scale using ethanol as the coupled substrate for recycling[9] catalytic amount of the nicotinamide coenzyme employed. Each reduction was stopped when GLC analysis showed it to be ~50% complete. The products were isolated by chloroform extraction and separated by column chromatography. The structures of the recovered ketones and the cis and trans alcohol products were identified by comparison with the racemic compounds characterized previously. The results of the preparative-scale HLADH-mediated reductions are summarized in Scheme II.

Enantiomeric Excess Determinations. The ee's (enantiomeric excesses) of the ketones **3a–d** recovered from the enzymic reactions were determined by their conversions to the ketals **4a–d** with (−)-(2*R*,3*R*)-2,3-butanediol followed by ^{13}C NMR analysis.[10] The diastereomeric ketals obtained from the racemic ketones were used as reference standards. The Δδ values observed for the diastereotopic carbon atoms of ketals (±)-**4a–d** are recorded in Table II. The ee levels of the *cis*- and *trans*-tetrahydropyranyl alcohols

Scheme II

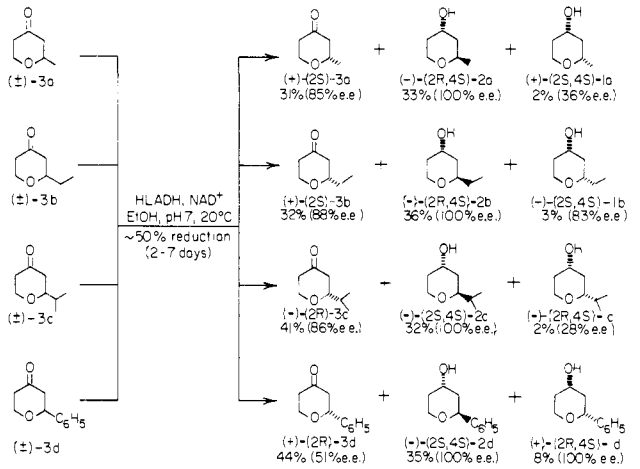
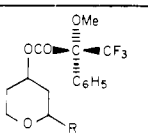
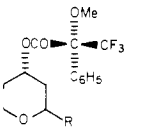


Table III. Enantiomeric Shift Differences for the Methoxyl Protons of the MTPA Esters **5a–d** and **6a–d**[a]

MTPA structure	compd	$Eu(fod)_3$, equiv	ΔΔδ, ppm
	(±)-**5a**	0.59	0.10
	(±)-**5b**	1.02	0.14
	(±)-**5c**	0.40	0.18
	(±)-**5d**	0.44	0.20
5			
	(±)-**6a**	0.50	0.28
	(±)-**6b**	0.13	0.11
	(±)-**6c**	0.17	0.36
	(±)-**6d**	0.30	0.32
6			

[a] Determined at 60 MHz in CCl_4.

of Scheme II were established by ^1H NMR examination in the presence of $Eu(fod)_3$ of the methoxyl protons of their MTPA esters **5a–d** and **6a–d**, respectively.[11] The ΔΔδ values observed for the MTPA esters of the racemic alcohols used as reference standards are given in Table III. For the enzymically derived trans alcohol esters **6a–c** and the cis-phenyl compound **5d**, only one methoxyl peak was observed, thus showing the compounds to be enantiomerically pure.[12] In contrast to the overlapping C-4, C-5, and, C-6 proton peak situation encountered with the parent alcohols (Figure 1), the ^1H NMR spectra of the pairs of MTPA esters **5a–d** and **6a–d** were distinctive in the C-4 region and corroborated the cis and trans assignments of **1a–d** and **2a–d** made on the basis of Figure 1.

Absolute Configuration Determinations. The absolute configuration assignments summarized in Scheme II were based on

(9) Zagalak, B.; Frey, P. A.; Karabatsos, G. L.; Abeles, R. H. *J. Biol. Chem.* **1966**, *241*, 3028.
(10) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183.
(11) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(12) The absence of C-2 epimers in these compounds was confirmed by a subsequent addition of ~5% of racemic ester to the NMR tube, whereupon the methoxyl peak corresponding to the other enantiomer became clearly visible.

octant rule[13] analyses of the negative Cotton effects observed for the ketones (−)-**3a–d** obtained on oxidation of the trans alcohols (−)-**2a–d**. For the thermodynamically preferred chair conformations of **3a–d**, the equatorially oriented C-2 substituents are positioned in negative octants only for (2*R*)-**3a,b** and (2*S*)-**3c,d**. This establishes the C-2 chiralites of the trans alcohols (−)-**2a–d** of Scheme II. The oxygen atom of the tetrahydropyran ring does not affect the octant rule analysis since the heteroatom is in the nodal plane of the carbonyl group and does not contribute to the rotatory strength. The C-2 configurations of the cis alcohols were determined by oxidation to the corresponding optically active tetrahydropyranones **3a–d** and comparison of the signs of their optical rotations with those of the ketones derived from the trans alcohols. The C-2 chiralities of (+)-**3a–d** recovered from the HLADH-catalyzed reductions were similarly identified. The C-4 configurations of the alcohols **1a–d** and **2a–d** (Scheme II) followed from the relative C-2 and C-4 configuration relationships imposed by the cis or trans orientations of the substituents at these positions.

Discussion

The preparations of the ketone substrates (±)-**3a–d** and of the cis and trans alcohols (±)-**1a–d** and (±)-**2a–d** were achieved without difficulty. As expected from the literature reports,[8] the cis isomers predominated in the mixture of alcohols obtained both from the Prins reaction (Scheme I) and by reduction of the ketones (±)-**3a–d**. Although the overlapping ^{1}H NMR resonances of the C-2, C-4, and C-6 protons precluded direct identification of the cis and trans alcohols **1a–d** and **2a–d**, the individual isomers were readily distinguished by the characteristic 3–5-ppm ^{1}H NMR patterns of each series of isomers (Figure 1). Subsequently, further confirmation of the correctness of these geometric isomer assignments was provided by the ^{1}H NMR spectra of the MTPA esters **5a–d** and **6a-d**, in which the C-4 proton patterns were no longer obscured. For the cis esters **5a–d**, the axial C-4 proton peaks were broad (~20-Hz half-width) and resonated ~0.2 ppm upfield from the narrower (~8-Hz half-width) bands of the corresponding equatorial protons of the trans isomers **6a–d**.[4b,8,14]

Each of the tetrahydropyranones (±)-**3a–d** was a good substrate of HLADH (Table I). The reduction rate of the parent ketone tetrahydropyran-4-one itself is significantly lower (14%) than that of the cyclohexanone reference. The reason for this diminished reaction rate is not clear since in this case the shapes and conformations of the carbocyclic and heterocyclic rings should be similar. However, transannular interactions between the oxygen heteroatom and the carbonyl group may be lowering its susceptibility to attack by the hydride equivalent of NADH. The introduction of C-2 substituents into the tetrahydropyran ring does not have any further deleterious effects. In fact, for (±)-**2d**, the C-2 phenyl group induces a remarkable acceleration in the rate of reduction.

The preparative-scale HLADH-catalyzed reductions proceeded smoothly. The usual simple experimental methodology and straightforward workup procedure were employed to give good recoveries of unchanged ketone and product alcohols from each reaction. The 66–87% yields cited in Scheme II refer to isolated, purified materials. The progress of each reduction was monitored by GLC. In accordance with our normal practice for racemic substrates,[4b] all reactions were terminated at the ~50% stage, the point at which enantiomerically specific enzyme-mediated resolutions would stop automatically.

The ee's of the recovered ketones and of the product alcohols were readily determined by the direct ^{13}C and ^{1}H NMR methods employed. The absolute configuration assignments were also straightforward.

For each of the ketones (±)-**3a–d**, HLADH-catalyzed reduction proceeds in the same absolute configuration sense to give the trans alcohols (−)-**2a–d** as the almost exclusive products. Furthermore, these alcohols, which arise from reduction of the (−)-**3a–d** enantiomers, are optically pure. The cis alcohols isolated, all of whose C-2 configurations are opposite to those of the corresponding trans products, are formed in very minor amounts via the much less preferred reduction of a small proportion of the (+)-**3a–d** stereoisomers. Because these latter reductions are so slow, most of the (+)-**3a–d** enantiomers are recovered (Scheme II). The <100% ee levels of the (+)-**3a–d** ketones largely reflect the consequences of incomplete reduction. The cis alcohols (+)-**1a**, and (−)-**1b,c** are also only partially optically pure. In this case, the formation of mixtures of enantiomers reflects the relative influences of thermodynamic and kinetic control factors.

For fast HLADH-catalyzed reductions, the stereochemistries of the products are those of the kinetically controlled reactions. However, during long reaction periods less preferred pathways can become significant as a result of the equilibrium nature of the C=O ⇌ CH(OH) oxidoreduction reaction and the eventual preference of thermodynamically preferred product geometries.[2a] The relative importance of these competitive pathways is discussed in detail later in the cubic-model analysis of the results.

The Scheme II results parallel those of the analogous carbocyclic[2a,15] and tetrahydrothiopyran[4b] ketone reductions.[16] The correspondence of the data for HLADH-catalyzed reductions of 3-substituted cyclohexanones[2a,15] with the data of this study is very close. This is as expected since the C–C and C–O[17] bond lengths (~1.5 Å) and C–C–C and C–O–C bond angles (~108–115°) do not differ significantly. In contrast, the proportion of cis alcohol products is much higher when 2-substituted tetrahydrothiopyran-4-ones are the substrates.[4b] However, the difference is one of degree only and is attributed to the distortion from cyclohexane or tetrahydropyran geometry induced by the longer C–S bond length (~1.8 Å) and the ~99° C–S–C bond angle.[18]

Cubic Active-Site Section Analysis. The stereospecificities of the Scheme II reactions are readily interpreted by using the HLADH active-site section based on cubic-space descriptors.[4a] The analysis for (±)-**3a** depicted in Figure 2 is representative of the basic procedure and is applicable to each of (±)-**3a–d**. The overwhelming predominance of the trans alcohol (2*R*,4*S*)-**2a** absolute configuration arises via reduction of conformation III of (2*R*)-**3a** as shown in Figure 2b. Only conformation III can bind in wholly allowed regions when forming a productive enzyme–substrate complex. All of the other conformations and orientations are unfavorable to a greater or lesser degree. Conformation I is precluded by a forbidden CH_3–E3,K6 interaction. Conformation II requires positioning of the methyl group in the underneath-the-section region below limited cube B2, designated as U(B2). The substrate-accommodating capacities of the underneath regions reflect the nature of the cubes above them.[4a] Accordingly, U(B2) is also "limited", and its occupation results in a markedly reduced rate of reduction. Cis alcohol (2*S*,4*S*)-**1a** is thus a minor product only. Reduction via conformation IV is even less favorable since it requires location of the CH_3 substituent in limited cube U(D2) and adjacent to forbidden region U(E2). The formation of (2*R*,4*R*)-**1a** by this route is thus extremely slow but is nevertheless finite. Its presence is reflected by its dilution of the enantiomeric purity of (2*S*,4*S*)-**1a** (Scheme II).

The fact that the cis alcohols (2*S*,4*S*)-**1a** and (2*R*,4*R*)-**1a** are produced at all is a consequence of the lengthy reaction period. This permits the products of the less facile reactions to form slowly.

(13) Moffitt, W.; Woodward, R. B.; Moscowitz, A.; Klyne, W.; Djerassi, C. *J. Am. Chem. Soc.* **1961**, *83*, 4013.

(14) Emsley, J. W.; Feeney, J.; Sutcliffe, L. H. In "High-Resolution Nuclear Magnetic Resonance Spectroscopy"; Pergamon: London, 1966; Vol. II, pp 696, 811.

(15) (a) Helmchen-Zeier, R. E. Thesis No. 4991, ETH, Zurich. (b) Reference 2a, pp 300–303.

(16) The configurations shown in ref 15b for *cis*-3-alkylcyclohexanol products were based on an interpretation of some rather ambiguous discussion in the original reference[15a] and are incorrect. The chiralities of the preferred cis alcohol products of HLADH-catalyzed reductions of 3-substituted cyclohexanones and their oxa and thia[4b] analogues are now considered to be of the same (Scheme II) absolute configuration sense in every way.

(17) Wheatley, P. J. In "Physical Methods in Heterocyclic Chemistry"; Katritzky, A. R., Ed.; Academic Press: New York, 1963; Vol. V, p 189.

(18) (a) Tagaki, W. In "Organic Chemistry of Sulfur"; Oae, S., Ed.; Plenum: New York, 1977; pp 245–247. (b) Marsh, R. E. *Acta Crystallogr.* **1955**, *8*, 91.

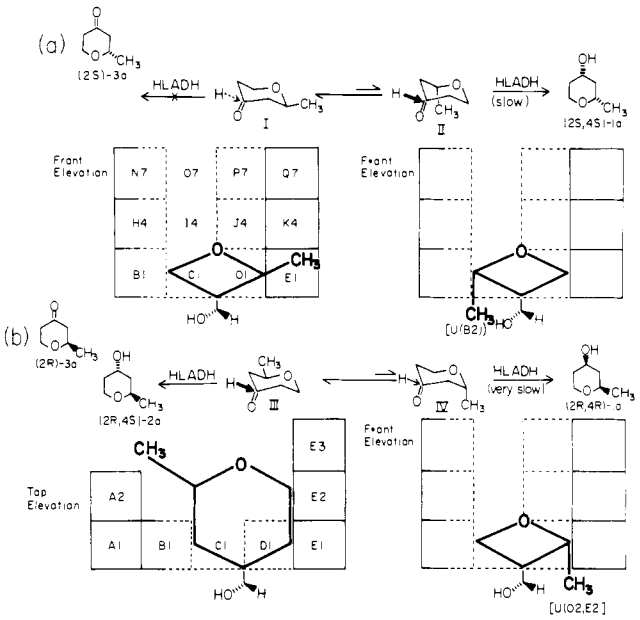


Figure 2. Cubic active-site section analysis of the substrate activity and product stereochemistry for HLADH-catalyzed reductions of (±)-**3a–d**. Each cube of the section is designated alphanumerically. In this figure, the top and front elevation perspectives[4a] are used to depict the best substrate orientations at the active site. The cube bounded by solid lines are forbidden regions where substrate binding is precluded, as is the front of the section, due to their being occupied by enzymic amino acid residues or by coenzyme. Those 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. 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. This is shown in its alcohol-like form since this is considered to resemble the transition state of the reaction. The various possible orientations of the substrate are then compared to identify the favored excited-state complexes, i.e., those with all groups in allowed regions. If a group must locate in a limited region for reduction to occur, the rate is slowed very markedly. Formation of a productive excited-state complex is precluded if any part of the substrate has to take up a position in a forbidden region when otherwise corectly oriented for reduction to take place. Full details of the model and its application are given in ref 4a. For the Scheme II substrates, the active-site binding and orientation of each chair conformation of each enantiomer must be analyzed. Part a covers reduction of enantiomers of the (2*S*)-**3a** absolute configuration series and part b those of the (2*R*)-**3a** type. The direction of hydride delivery is indicated by the broken and solid arrows for the unreactive and reactive substrate orientations, respectively. The orientations shown are the most favorable of the many possibilities. (a) Reduction via conformation I of (2*S*)-**3a** is precluded because the alkyl group would have to occupy forbidden cubes *E*3 and *K*6. Conformation II can be positioned in allowed space except for the U(B2) location of the methyl group. This is a limited region, and its occupation slows down the reaction rate considerably. (2*S*,4*S*)-**1a** is therefore a minor product only. (b) Reduction via conformation IV of (2*R*)-**3a** is slower still because the CH_3 must be placed in the even less accomodating limited (bordering on forbidden) U(D2,E2) region. Only for conformation III is binding in wholly allowed regions possible. This results in facile reduction to the major trans alcohol product (2*R*,4*S*)-**2a** as shown.

Also, because CH(OH) ⇌ C=O equilibration is possible under the reaction conditions,[2a,4c] gradual accumulation of the thermodynamically preferred cis alcohols rather than their trans isomers is eventually favored. However, when the C-2 substituent is phenyl, as for (±)-**3d**, binding of conformation IV as shown in Figure 2b is precluded by the intrusion of the large C_6H_5 group into forbidden cube U(E2). This prevents reduction of (2*S*)-**3d** to (2*S*,4*R*)-**1d** from taking place, and the cis alcohol (2*R*,4*S*)-**1d** formed via the conformation II reduction mode (Figure 2a) remains enantiomerically pure.

The current results, and those obtained previously on hemiacetal oxidations,[4d] show that the introduction of oxygen as a heteroatom into monocyclic substrates does not alter the expected course or basic efficiency of HLADH catalysis. Further studies delineating the scope of preparative-scale HLADH-catalyzed oxidoreductions of oxygen-containing alcohols and ketones are in progress.

Experimental Section

IR (as films) and NMR (in C^2HCl_3 unless otherwise specified) spectra were recorded for each compound. The spectra were all in accord with the structures assigned, and only selected data are reported. IR spectra were recorded on a Unicam SP3-200 spectrometer. ^1H NMR spectra were determined at 60 MHz on a Varian T-60 spectrometer and ^{13}C NMR spectra were obtained on a CFT-20 spectrometer with $(CH_3)_4Si$ as reference. GLC analyses were performed on 3% OV101 or QF1 columns with flame ionization detection. Cis: trans isomer ratios were determined by column chromatographic separations on silica gel. Optical rotations were measured in $CHCl_3$ with a Perkin-Elmer 141 polarimeter, and CD spectra were recorded on a Jasco J-41A instrument. The UV absorptions of the enzymic relative-rate studies were monitored on a Unicam SP 1800 spectrophotometer. NAD^+ was obtained from Kyowa Hakko Co., NY. HLADH (E.C. 1.1.1.1) was purchased from Sigma, the activity being determined[19] prior to use. The amounts of HLADH quoted refer to milligrams of active enzyme.

Preparations of 2-Substituted Tetrahydropyranones (±)-3a–d. The ketones (±)-**3a–d** were prepared by oxidation of the corresponding cis–trans mixtures of the tetrahydropyranols **1a–d** and **2a–d** obtained by condensation of the appropriate aldehyde with 3-butenol[20] by the method of Hanschke[7] as follows: 2-methyltetrahydropyran-4-ol ((±)-**1a** and (±)-**2a**, ~20:1, 68% yield): bp 90 °C (5 mmHg) (lit.[7] bp 99 °C (20 mmHg)); 2-ethyltetrahydropyran-4-ol ((±)-**1b** and **2b**, ~20:1, 72% yield): bp 90 °C (2 mmHg) (lit.[7] bp 108 °C (16 mmHg)); 2-isopropyltetrahydropyran-4-ol[21] ((±)-**1c** and (±)-**2c**, ~20:1, 75% yield): bp 115 °C (4 mmHg); 2-phenyltetrahydropyran-4-ol ((±)-**1d** and (±)-**2d**, ~4:1, 60% yield): bp 102 °C (0.2 mmHg) (lit.[7] bp 142–143 °C (0.5 mmHg)).

2-Ethyltetrahydropyran-4-one ((±)-3b). Finely divided pyridinium chlorochromate[22] (13.6 g, 1.5 equiv) was added at 20 °C to a stirred solution of 2-ethyltetrahydropyran-4-ol ((±)-**1b** and (±)-**2b**, 5.2 g, 0.04 mol) in dry CH_2Cl_2 (80 mL). When TLC analysis showed the reaction to be complete (2–3 h), hexane (80 mL) and ether (80 mL) were added. The mixture was filtered through Celite, and the black residue was triturated repeatedly with ether until it became granular. The combined organic solvents were rotoevaporated, and the residual oil was Kugelrohr distilled to give the ketone (±)-**3b** as a colorless oil (3.9 g, 76% yield): bp 60 °C (4 mmHg) (lit.[7] bp 81 °C (12 mmHg)); IR 1720 cm^{-1}; ^1H NMR δ 0.98 (3 H, *t*, *J* = 6 Hz), 1.56 (2 H, q, *J* = 6 Hz), 2.20–2.70 (4 H, m), 3.40–3.90 (2 H, m), and 4.12–4.50 (1 H, m).

The other tetrahydropyranones were prepared by the same procedure:

2-Methyltetrahydropyran-4-one ((±)-3a) (from (±)-**1a** and (±)-**2a**): 83% yield; bp 70 °C (5 mmHg) (lit.[7] bp 70 °C (20 mmHg)); IR 1718 cm^{-1}; ^1H NMR δ 1.30 (3 H, d, *J* = 6.5 Hz), 2.40–2.90 (4 H, m), and 3.45–4.50 (3 H, m).

2-Isopropyltetrahydropyran-4-one ((±)-3c) (from (±)-**1c** and (±)-**2c**): 82% yield; bp 60 °C (1 mmHg) (lit.[21] bp 64–65 °C (3 mmHg)); IR 1720 cm^{-1}; ^1H NMR δ 0.90, 1.02 (6 H, dd, *J* = 2.5 Hz), 1.50–1.98 (1 H, m), 2.23–2.50 (4 H, m), 3.11–3.80 (2 H, m), and 4.10–4.47 (1 H, m).

2-Phenyltetrahydropyran-4-one ((±)-3d) (from (±)-**1d** and (±)-**2d**): 72% yield; bp 120 °C (4 mmHg) (lit.[7] bp 102–104 °C (0.1 mmHg)); IR 1720 cm^{-1}; ^1H NMR δ 2.37–2.87 (4 H, m), 3.50–4.72 (3 H, m), and 7.33 (5 H, s).

Preparation of Cis and Trans Alcohols (±)-1a–d and (±)-2a–d. Mixtures of cis and trans alcohols (±)-**1a–c** and (±)-**2a–c** were obtained in quantitative yields by reduction of the corresponding ketones (±)-**3a–c** with $NaBH_4$ (2 equiv) in 2-propanol[8] (for **1a** and **2a**) or by hydrogenation in ethanol in the presence of platinum[8] (for **1b,c** and **2b,c**). For (±)-**1d** and (±)-**2d** the cis–trans mixture obtained above from the Scheme I reaction was employed directly. The isomers were separated by chromatography on silica gel with hexane–ether elution, with the trans alcohols being eluted first in each case as follows:

***cis*- and *trans*-2-Methyltetrahydropyran-4-ol ((±)-1a and (±)-2a).** Cis–trans (10:1) mixture separated with hexane–ether (3:2) elution cis isomer (±)-**1a**, ^1H NMR δ 1.03–2.10 (7 H, m including d, *J* = 6 Hz), 2.90 (H, br s), and 3.10–4.20 (4 H, m); trans isomer (±)-**2a**, ^1H NMR

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δ 1.13 (3 H, d, J = 5 Hz), 1.30–2.23 (4 H, m), 2.62 (1 H, s), and 3.53–4.27 (4 H, m).

***cis*- and *trans*-2-Ethyltetrahydropyran-4-ol ((±)-1b and (±)-2b).** Cis:trans (5:1) mixture separated with hexane–ether (1:1) elution: cis isomer (±)-**1b**, ^{1}H NMR δ 0.73–2.17 (9 H, m, containing δ 0.95 (3 H, t, J = 9 Hz) and 1.25 (2 H, q, J = 9 Hz)), 2.30 (1 H, br s), and 2.93–4.20 (4 H, m); trans isomer (±)-**2b**, ^{1}H NMR δ 0.70–2.20 (10 H, m containing δ 0.95 (3 H, t, J = 8 Hz), 1.22 (2 H, q, J = 8 Hz), and 1.95 (1 H, s, OH)), 3.50–4.01 (3 H, m), and 4.13–4.37 (1 H, m).

***cis*- and *trans*-2-Isopropyltetrahydropyran-4-ol ((±)-1c and (±)-2c).** Cis–trans (4:1) mixture separated with hexane–ether (1:1) elution: cis isomer (±)-**1c**, ^{1}H NMR δ 0.87 (3 H, d, J = 3 Hz), 0.98 (3 H, d, J = 3 Hz), 1.17–2.13 (5 H, m), 2.69 (1 H, s), 2.78–4.20 (4 H, m); trans isomer (±)-**2c**, ^{1}H NMR δ 0.90 (3 H, d, J = 3 Hz), 0.98 (3 H, d, J = 3 Hz), 1.23–2.02 (6 H, m, including δ 1.68 (1 H, s, OH)), 3.27–4.00 (3 H, m), and 4.11–4.39 (1 H, m).

***cis*- and *trans*-2-Phenyltetrahydropyran-4-ol ((±)-1d and (±)-2d).** Cis–trans (4:1) mixture separated with hexane–ether (2:1) elution: cis isomer (±)-**1d**, ^{1}H NMR δ 1.10–2.53 (5 H, m, including δ 2.00 (1 H, br s, OH)), 3.29–4.43 (4 H, m), and 7.29 (5 H, s); trans isomer (±)-**2d**, ^{1}H NMR δ 1.57–2.56 (5 H, m, including δ 2.40 (1 H, br s, OH)), 3.80–4.47 (3 H, m), 4.80 (1 H, t, J = 7 Hz), and 7.28 (5 H, s).

The characteristic cis and trans ^{1}H NMR patterns of the 3–5-ppm regions are reproduced in Figure 1.

Relative Rates of HLADH-Catalyzed Reductions of (±)-3a–d. The assays were carried out as described previously[4b] on solutions 10^{-2} M in (±)-**3a–c** and 8×10^{-3} M for the less soluble (±)-**3d**. The results are summarized in Table I.

Preparative-Scale HLADH-Catalyzed Reductions of (±)-3a–d. All reductions were carried out by the same general procedure. The tetrahydropyranone substrate (2 g) was dissolved or suspended in 0.1 M potassium phosphate buffer (pH 7, 1 L or up to 2 L for the more insoluble ketone (±)-**3d**) at 20 °C. NAD^+ (1.5 g) and ethanol (3 mL) were then added, and the pH was readjusted to 7 with 10 M aqueous KOH. The reaction was initiated by the addition of HLADH (50 mg). Further 10-mg portions of enzyme were added every 24 h. The extent of reaction was monitored by GLC. After 50% reduction had occurred (2–7 days), NaCl was added to saturate the solution, and the mixture was then continuously extracted with $CHCl_3$ for 24 h. The dried ($MgSO_4$) $CHCl_3$ extract was rotoevaporated and the residue chromatographed on silica. The unchanged ketone, trans alcohol, and cis alcohol were eluted in that order by using the hexane–ether solvent system cited in the racemic cis and trans alcohol separations described above. Each ketone and alcohol product was then Kugelrohr distilled. The IR and ^{1}H NMR spectral properties of each compound were identical with those of the corresponding racemates recorded earlier in this section.

The individual reactions gave the following results (cf. Scheme II).

Reduction of (±)-3a for 2 days yielded (±)-(2*S*)-**3a** (620 mg, 31% yield, 85% ee, $[\alpha]^{25}_D$ +10.9° (c 1, $CHCl_3$)), (−)-(2*R*,4*S*)-**2a** (655 mg, 33% yield, 100% ee, $[\alpha]^{25}_D$ −8.75° (c 1.2, $CHCl_3$)), and (+)-(2*S*,4*S*)-**1a** (44 mg, 2% yield, 36% ee, $[\alpha]^{25}_D$ +1.6° (c 0.44, $CHCl_3$)).

Reduction of (±)-3b for 7 days gave (+)-(2*S*)-**3b** (627 mg, 32% yield, 88% ee, $[\alpha]^{25}_D$ +16.6° (c 1.1, $CHCl_3$)), (−)-(2*R*,4*S*)-**2b** (721 mg, 36% yield, 100% ee, $[\alpha]^{25}_D$ −2.26° (c 1, $CHCl_3$)), and (−)-(2*S*,4*S*)-**1b** (49 mg, 2.5% yield, 83% ee, $[\alpha]^{25}_D$ −2.2° (c 0.45, $CHCl_3$)).

Reduction of (±)-3c for 3 days afforded (+)-(2*R*)-**3c** (817 mg, 41% yield, 86% ee, $[\alpha]^{25}_D$ +16.3° (c, 1, $CHCl_3$)), (−)-(2*S*,4*S*)-**2c** (636 mg, 32% yield, 100% ee, $[\alpha]^{25}_D$ −10.4° (c, 1, $CHCl_3$)), and (−)-(2*R*,4*S*)-**1c** (34 mg, 1.7% yield, 28% ee, $[\alpha]^{25}_D$ −0.4° (c 0.23, $CHCl_3$)).

Reduction of (±)-3d yielded (+)-(2*R*)-**3d** (883 mg, 44% yield 51% ee, $[\alpha]^{25}_D$ +49.2° (c 1, $CHCl_3$)), (−)-(2*S*,4*S*)-**2d** (701 mg, 35% yield, 100% ee, $[\alpha]^{25}_D$ −50.8° (c, 1, $CHCl_3$)), and (+)-(2*R*,4*S*)-**1d** (166 mg, 8% yield, 100% ee, $[\alpha]^{25}_D$ +39.8° (c 0.4, $CHCl_3$)).

Enantiomeric Excess Determinations of 3a–d Recovered from HLADH-Catalyzed Reductions. The optically active ketones **3a–d** and, for reference, their racemic counterparts were converted to the corresponding ketals **4a–d** with (−)-(2*R*,3*R*)-2,3-butanediol by the general procedure reported previously.[4b]

The ^{1}H-decoupled ^{13}C NMR spectrum of each was determined. The ee values of the ketals derived from optically active **3a–d** were then determined from their ^{13}C NMR spectra[10] by direct measurement of the signal intensities of the selected diastereotopic carbon atoms whose enantiomeric shift differences are indicated in Table II. The e.e. values observed are summarized in Scheme II. The ^{13}C NMR data for the racemic ketals are as follows:

2-Methyltetrahydropyran-4-one Ketal (±)-4a: bp 62 °C (3 mmHg); ^{13}C NMR δ 16.95 (C-8), 21.64 and 21.77 (C-2, CH_3), 36.47 and 37.54 (C-5), 44.29 and 45.26 (C-3), 65.17 and 65.38 (C-6), 71.38 and 71.67 (C-2), 77.93 and 78.30 (C-7), and 105.85 (C-4).

2-Ethyltetrahydropyran-4-one Ketal (±)-4b: bp 70 °C (4 mmHg); ^{13}C NMR δ 9.71 (CH_2CH_3), 16.83 and 16.95 (C-8), 28.94 and 29.03 (CH_2CH_3), 36.80 and 37.88 (C-5), 42.21 and 43.20 (C-3), 65.17 and 65.41 (C-6), 76.59 and 76.94 (C-2), 77.93 and 78.20 (C-7), and 106.04 (C-4).

2-Isopropyltetrahydropyran-4-one Ketal (±)-4c: bp 80 °C (3 mmHg); ^{13}C NMR δ 16.90 and 17.03 (C-8), 18.27 ($CH(CH_3)_2$), 32.87 ($CH(CH_3)_2$), 36.91 and 37.98 (C-5), 39.41 and 40.42 (C-3), 65.23 and 65.47 (C-6), 77.92 and 78.34 (C-2), 80.17 and 80.48 (C-7), and 106.35 (C-4).

2-Phenyltetrahydropyran-4-one Ketal (±)-4d purified by chromatography on silica gel with hexane–ether (7:2) elution: ^{13}C NMR δ 16.91 (C-8), 36.62 and 37.65 (C-5), 44.24 and 45.26 (C-3), 65.71 and 65.92 (C-6), 77.44 and 77.78 (C-2), 78.07 and 78.42 (C-7), 105.85 (C-4), and 125.98, 126.47, 128.32, 142.03, and 142.14 (C_6H_5).

Enantiomeric Excess Determinations of 1a–d and 2a–d Products of HLADH-Catalyzed Reductions. The optically active and racemic reference alcohols **1a–d** and **2a–d** (0.1 mmol) were converted into their respective MTPA esters **5a–d** and **6a–d** in quantitative yields by the standard literature procedure[11] with freshly prepared (+)-(2*S*)-α-methoxy-α-(trifluoromethyl)-α-phenylacetyl chloride (1.1 equiv), $[\alpha]^{25}_D$ +126.0° (c 3.3, CCl_4) (lit.[11] $[\alpha]_D$ 129.0° (c 5.17, CCl_4). The ee levels of the HLADH-derived MTPA esters were determined by 60-MHz ^{1}H NMR (in CCl_4) examination of the methoxyl protons in the presence of Eu(fod)$_3$ shift reagent, using the racemic esters as reference standards for the ΔΔδ values for each pair of diastereotopic methoxy groups (recorded in Table III). The ee values measured are summarized in Scheme II. The C-4 regions of the ^{1}H NMR spectra of the MTPA esters **5a–d** and **6a–d** were used to corroborate the cis and trans relative-configuration assignments of **1a–d** and **2a–d**, respectively. The ^{1}H NMR (in CCl_4) spectral data for the C-4 regions are recorded below.

Cis Series. MTPA Esters 5a–d. (±)-**5a** ^{1}H NMR δ 5.0 (1 H, m, $W_{1/2}$ = 20 Hz, C-4H); (±)-**5b**: ^{1}H NMR δ 5.01 (1 H, m, $W_{1/2}$ = 22 Hz, C-4H); (±)-**5c**: ^{1}H NMR δ 5.03 (1 H, m, $W_{1/2}$ = 22 Hz, C-4H); (±)-**5d**: ^{1}H NMR δ 5.08 (1 H, m, $W_{1/2}$ = 22 Hz, C-4H).

Trans Series. MTPA Esters 6a–d. (±)-**6a**: ^{1}H NMR δ 5.17 (1 H, m, $W_{1/2}$ = 8 Hz, C-4H); (±)-**6b**: ^{1}H NMR δ 5.18 (1 H, m, $W_{1/2}$ = 9 Hz, C-4H); (±)-**6c**: ^{1}H NMR δ 5.17 (1 H, m, $W_{1/2}$ = 8 Hz, C-4H); (±)-**6d**: ^{1}H NMR δ 5.20 (1 H, m, $W_{1/2}$ = 8 Hz, C-4H).

Absolute Configuration Determinations. The chiral alcohols (−)-**2a–d**, (+)-**1a,d**, and (−)-**1b,c** were oxidized to the corresponding ketones **3a–d** with pyridinium chlorochromate as described above in the preparation of (±)-**3a–d**. Their absolute configurations, and those of the ketones (+)-**3a–d** recovered directly from the HLADH-catalyzed reductions, were assigned by comparison of their signs of optical rotation with those of (−)-(2*R*)-**3a,b** and (−)-(2*S*)-**3c,d**. The absolute configurations of the latter, obtained from oxidation of the 100% ee trans alcohols (−)-**2a,b**, were determined by octant rule[13] analysis of their CD spectra. With the absolute configuration at C-2 established, the C-4 chiralities of the enzymically derived trans and cis alcohols **1a–d** and **2a–d** followed from the relative configurations of C-2 and C-4 in the two series. The data used are as follows:

Oxidation of Trans Alcohols. (−)-**2a** gave (−)-(2*R*)-**3a**: $[\alpha]^{25}_D$ −19.9° (c 0.78, $CHCl_3$); CD (c 0.004 M, EtOH, 20 °C) $[\theta]_{330}$ 0°, $[\theta]_{292}$ −1550°, $[\theta]_{230}$ 0°. (−)-**2b** gave (−)-(2*R*)-**3b**: $[\alpha]^{25}_D$ −18.6° (c 1.12, $CHCl_3$); CD (c 0.004 M, EtOH, 20 °C) $[\theta]_{330}$ 0°, $[\theta]_{291}$ −3050°, $[\theta]_{240}$ 0°. (−)-**2c** gave (−)-(2*S*)-**3c**: $[\alpha]^{25}_D$ −24.8° (c 1.3, $CHCl_3$); CD (c 0.004 M, EtOH, 20 °C) $[\theta]_{335}$ 0°, $[\theta]_{290}$ −3550°, $[\theta]_{230}$ 0°. (−)-(2*S*)-**2d** gave (−)-(2*S*)-**3d**: $[\alpha]^{25}_D$ −80.0° (c, 1.0, $CHCl_3$); CD (c 0.004 M, EtOH, 20 °C) $[\theta]_{330}$ 0°; $[\theta]_{286}$ −4500°, $[\theta]_{240}$ 0°.

Oxidation of Cis Alcohols. (+)-**1a** gave (+)-(2*S*)-**3a**: $[\alpha]^{25}_D$ +2.4° (c 0.8, $CHCl_3$); (−)-**1b** gave (+)-(2*S*)-**3b**: $[\alpha]^{25}_D$ +2.7° (c 0.11, $CHCl_3$); (−)-**1c** gave (+)-(2*R*)-**3c**: $[\alpha]^{25}D$ + 2.5° (c 0.85, $CHCl_3$); (+)-**1d** gave (+)-(2*R*)-**3d**: $[\alpha]^{25}_D$ +77.4° (c 1.04, $CHCl_3$).

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Registry No. (±)-**1a**, 82065-16-5; (+)-(2*S*,4*S*)-**1a**, 82110-13-2; (±)-**1b**, 82065-17-6; (−)-(2*S*,4*S*)-**1b**, 82110-14-3; (±)-**1c**, 82065-18-7; (−)-(2*R*,4*S*)-**1c**, 82110-15-4; (±)-**1d**, 82065-19-8; (+)-(2*R*,4*S*)-**1d**, 82110-16-5; (±)-**2a**, 82065-20-1; (−)-(2*R*,4*S*)-**2a**, 82110-17-6; (±)-**2b**, 82065-21-2; (−)-(2*R*,4*S*)-**2b**, 82110-18-7; (±)-**2c**, 82065-22-3; (−)-(2*S*,4*S*)-**2c**, 82110-19-8; (±)-**2d**, 82065-23-4; (−)-(2*S*,4*S*)-**2d**, 82110-20-1; (±)-**3a**, 82065-24-5; (+)-(2*S*)-**3a**, 82110-21-2; (−)-(2*R*)-**3a**, 82110-22-3; (±)-**3b**, 82065-25-6; (+)-(2*S*)-**3b**, 82110-23-4; (−)-(2*R*)-**3b**, 82110-24-5; (±)-**3c**, 82065-26-7; (+)-(2*R*)-**3c**, 82110-25-6; (−)-(2*S*)-**3c**, 82110-26-7; (±)-**3d**, 82065-27-8; (+)-(2*R*)-**3d**, 82110-27-8; (−)-(2*S*)-**3d**, 82110-28-9; **4a**, 82065-28-9; (2*R*)-**4a**, 82110-29-0; (2*S*)-**4a**, 82110-30-3; **4b**, 82065-29-0; (2*R*)-**4b**, 82110-31-4; (2*S*)-**4b**, 82110-32-5; **4c**, 82065-

30-3; (2R)-**4c**, 82110-33-6; (2S)-**4c**, 82110-34-7; **4d**, 82065-31-4; (2R)-**4d**, 82110-35-8; (2S)-**4d**, 82110-36-9; (2R,4R)-**5a**, 82065-32-5; (2S,4S)-**5a**, 82065-33-6; (2R,4R)-**5b**, 82065-34-7; (2S,4S)-**5b**, 82065-35-8; (2R,4R)-**5c**, 82065-36-9; (2S,4S)-**5c**, 82065-37-0; (2R,4R)-**5d**, 82065-38-1; (2S,4S)-**5d**, 82065-39-2; (2R,4S)-**6a**, 82065-40-5; (2S,4R)-**6a**, 82065-41-6; (2R,4S)-**6b**, 82065-42-7; (2S,4R)-**6b**, 82065-43-8; (2R,4S)-**6c**, 82065-44-9; (2S,4R)-**6c**, 82065-45-0; (2R,4S)-**6d**, 82065-46-1; (2S,4R)-**6d**, 82065-47-2; (−)-(2R,3R)-2,3-butanediol, 24347-58-8; (+)-(2S)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 20445-33-4.

Communications to the Editor

Observations on the Geometry of Hydrogen Transfer in [1,5] Sigmatropic Rearrangements

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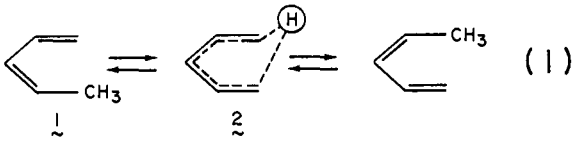
A [1,5] sigmatropic hydrogen-transfer process[1] must possess a six-membered pericyclic[2] transition state (TS‡) in accordance with the requirements of orbital symmetry conservation.[1] The validity of this regulation has been repeatedly confirmed[3] for retroene reactions in which either an O–H or a C–H bond has undergone suprafacial, linear hydrogen transfer to a carbon center in the pericyclic array. The criterion applied to assess the occurrence of concerted, linear H transfer was the temperature dependence of the primary H–D isotope effect.[4–11] Consistent with transition-state-derived theory,[12] a symmetrical or concerted[13] TS‡ will tend to exhibit an activation-energy difference between corresponding H and D bonds equal to their ground-state zero-point energy difference, i.e., $[\Delta E_a]_D^H \simeq [\Delta E_0]_D^H$, and a frequency factor ratio of no greater value than $2^{1/2}$, or, as established by model calculations,[14] $0.7 << A_H/A_D << 1.2$. Nonetheless, examples can be found in the literature where a 1,5 sigmatropic rearrangement of hydrogen has been depicted with a TS‡ of nonlinear H-transfer.

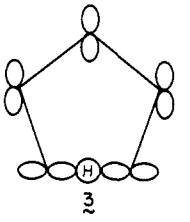
An exemplary case in point is that of the rearrangement of the pentadiene **1** shown[15] in eq 1, in which the temperature dependence



(1)

1 **2**

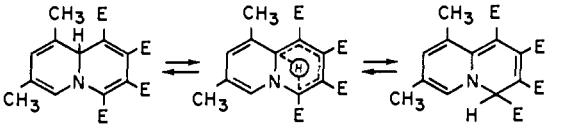
of k_H/k_D has been determined over a considerable temperature range, and the isotope effect parameters are reported to be $[\Delta E_a]_D^H \simeq 1.4$ kcal/mol and $A_H/A_D = 1.15$. When corrected for the α-secondary deuterium isotope effects, these values are closely coincident with expectations for a concerted, linear H-transfer mechanism. However, the authors[15] represented this pericyclic process with a bent TS‡ (**2**) in eq 1. Though they took note of the symmetry features of the TS‡ in keeping with the isotope effect results, they failed to recognize that these results also demanded a linear H-transfer TS‡. Apparently, the acyclic structure of conjugated double bonds in their cisoid conformation is capable of sufficient distention to permit linear H transfer, the minimum-energy configuration of this sigmatropic TS‡, as shown in **3**. The present investigation was undertaken with the objective



3

of identifying a [1,5] sigmatropic rearrangement occurring in a cyclic system which is not capable of such distention of the π framework.

The case chosen for study was the rearrangement of the 9a*H*-quinolizine (**4**) to the 4*H*-quinolizine (**5**) expressed in eq 2. The



(2)

4 **4a** **5**

Where E = −COOMe

temperature dependence of the isotope effect was again applied as the criterion of TS‡ geometry in H transfer. It has frequently been demonstrated, though not directly derivable (at present) from conventional transition-state theory of the isotope effect,[12] that a bent TS‡, i.e., one involving H transfer at an acute angle, can be correlated with a temperature-independent k_H/k_D. That is to say, the finding of isotope effect parameters of $[\Delta E_a]_D^H \simeq 0$ and $A_H/A_D >> 1.2$ has been empirically shown[17] to be most congruent with a bent TS‡.

The manner in which the isotope effect data for the reaction of eq 2 have been run, as well as the data gathered in these experiments, is presented in Table I. The determination that

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