to a stirred mixture of sodium metaperiodate (10.13 g, 47 mmol), water (40 mL), carbon tetrachloride (40 mL), and acetonitrile (60 mL). After 30 min, oxazolone (+)-11 (500 mg, 3.3 mmol) in 2 mL of acetonitrile was added.[20] After 2 h at room temperature, the mixture was evaporated to dryness (Rotavap) and the solid residue was extracted three times with hot ethyl acetate (50-mL portions). The yield of 4-carboxy-2-oxazolidone was 64 mg. This crude compound had $[\alpha]^{25}_D$ −14.0° (c 0.64, H_2O). The rotation of the same acid obtained by phosgenation of L-serine has been reported as $[\alpha]^{25}_D$ −17°,[21] thus establishing the S,D absolute stereochemistry for (+)-11.

Methyl 2,3,6-Trideoxy-L-hex-2-enopyranosid-4-ulose (4 and 5). To a solution of (S)-1 (0.5 g, 4 mmol) in a mixture of anhydrous ether (2 mL) and absolute methanol (3 mL) kept at 23 °C (dry ice–hexanes) was added bromine (1 g, 5 mmol) in MeOH (4 mL) gradually with stirring. The reaction mixture was stirred for another 30 min, then saturated with gaseous NH_3 to pH 8, and allowed to warm to room temperature. After filtration to remove NH_4Br, the solution was filtered off and was evaporated to give 0.5 g of compound 2 (85% yield): ^1H NMR ($CDCl_3$) δ 6.22 (m, 1 H), 5.79 (m, 1 H, 4.62 (s, 1 H), 4.38 (m, 1 H), 3.80 (m, 1 H), 3.20, (d, 3 H), 3.10, (d, 3 H), 1.38 (m, 3 H). Crude 2 (0.5 g) prepared above was dissolved in 2% H_2SO_4 (2 mL) and the solution left for 90 min at room temperature. The reaction mixture was brought to pH 4 with $NaHCO_3$. Water was removed in vacuo below 30 °C and the residue dissolved in 20 mL of ether. The ether was dried ($MgSO_4$) and evaporated to give 3: ^1H NMR δ 6.88 (m, 1 H), 6.08 (m, 1 H), 5.58 (m, 1 H), 4.64 (m, 1 H), 3.90 (br, 1 H) 1.32 (d, 3 H). A solution of 3 (0.6 g) and methyl orthoformate (0.32 g, 5 mmol) in absolute ether (20 mL) was chilled to 0 °C and 5 drops of $SnCl_4$ slowly added with stirring. After 45 min the reaction was quenched with triethylamine. The ethereal layer was washed three times with water and dried with anhydrous $MgSO_4$. Evaporation of solvent left 0.22 g of crude product which was purified by silica gel chromatography (2 × 50 cm) with CH_2Cl_2 as eluent. Fractions of the major component (R_f 0.45) were collected to give 0.23 g of 4 and 5 in a 2/1 ratio: ^1H NMR ($CDCl_3$) δ 6.88 (m, 1 H), 6.10 (m, 1 H), 5.28 (s, β-1H), 5.08 (d, α-1H), 3.52 (s, β-3H), 3.50 (s, α-3H), 1.50 (d, β-3H), 1.38 (d, α-3H); ^{13}C NMR ($CDCl_3$) δ 146.43 (C-3), 143.15 (C-2), 96.70 (β, C-1), 94.34 (α, C-1), 75.29 (β, 1c), 55.39 and 55.93 (OCH_3), 17.09 (C-6). Anal. Calcd for $C_7H_{10}O_3$: C, 59.12; H, 7.10. Found: C, 59.20; H, 7.11.

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Enzymes in Organic Synthesis. 41.[1] Stereoselective Horse Liver Alcohol Dehydrogenase Catalyzed Reductions of Heterocyclic Bicyclic Ketones[2]

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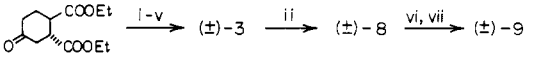
Preparative-scale horse liver alcohol dehydrogenase catalyzed reductions of racemic cis and trans bicyclic O- and S-heterocyclic ketones proceed with high enantiomeric selectivity. The diastereotopic selectivity for the pro-R faces of the carbonyl groups is also very high. The ee's of all but one of the product alcohols are >97%. The ee's of the recovered ketones are in the 52–60% range. The results confirm that an ether-oxygen or -sulfur substituent does not alter the enzyme's overall structural specificity or stereospecificity toward its ketone substrates.

While the application of enzymes in asymmetric synthesis is now well-documented, it remains a rapidly developing field.[3] One of the most versatile enzymes in this regard is horse liver alcohol dehydrogenase (HLADH[4]), which is a commercially available nicotinamide cofactor dependent enzyme that catalyzes stereospecific C=O ⇌ CH(OH) interconversions of a broad structural range of ketone and alcohol substrates.[2a,5] So far, relatively few HLADH-specificity studies have included substrates containing heteroatoms.[6] The present study examines the

Scheme I[a]



[a] (i) H^+, $HC(OEt)_3$; (ii) $LiAlH_4$; (iii) TsCl, pyr; (iv) Na_2S; (v) H^+, H_2O; (vi) Ph_3P, $C_6H_5CO_2H$, DEAD; (vii) $Ba(OH)_2$.

Table I. Relative Rates[a] of HLADH-Catalyzed Reductions of (±)-1–3

substr	rel rate	substr	rel rate
cyclohexanone	100	(±)-2	53
(±)-1	9	(±)-3	1.4

[a] Reduction rates were measured spectrophotometrically at 25 °C in 0.1 M phosphate buffer (pH 7) with [S] > 2 × 10^{-2} M and [NADH] = 1.75 × 10^{-4} M.

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(4) Abbreviations used: HLADH, horse liver alcohol dehydrogenase; $Eu(fod)_3$, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium(III); MTPA, (+)-(2R)-α-methoxy-α-(trifluoromethyl)-α-phenylacetate; NADH, reduced form of nicotinamide adenine dinucleotide.
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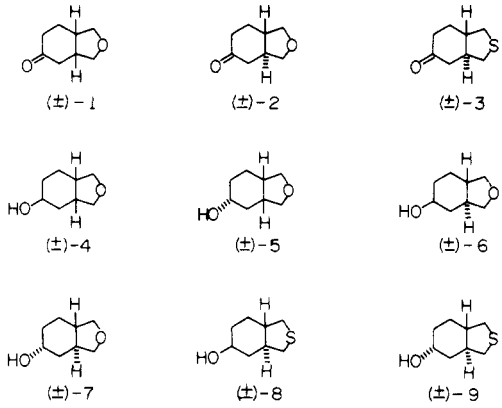
Table II. Results of HLADH-Catalyzed Reductions of Oxa- and Thiaketones (±)-1-3[a]

substr	extent of redctn (%)	products (% yield, % ee[b])
(±)-1	44	(+)-(1*S*,6*R*)-**1** (51, 52)
		(+)-(1*R*,3*S*,6*S*)-**4** (17,[c] 93)
		(1*R*,3*R*,6*S*)-**5** (5,[c] 19)
(±)-2	40	(−)-(1*S*,6*S*)-**2** (48, 60)
		(+)-(1*R*,3*S*,6*R*)-**7** (26, >97)
(±)-3	50	(+)-(1*S*,6*S*)-**3** (52, 53)
		(+)-(1*R*,3*S*,6*R*)-**9** (33, >97)

[a] In 0.1 M phosphate buffer (pH 7) at 20 °C for 2–5 days. [b] Error limits ±3%. [c] After purification by GLC.

influence of oxygen and sulfur heteroatoms on the HLADH-catalyzed reductions of the racemic bicyclic ketones (±)-**1–3**.



Results

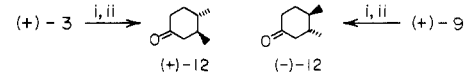
The oxa ketones (±)-**1,2** were prepared by combinations of literature methods, with the racemic 3β and 3α alcohols (±)-**4–7** required as product reference standards being obtained as intermediates in the synthesis. The corresponding thia compounds (±)-**3,8,9** were obtained as shown in Scheme I.

Each of (±)-**1–3** was a reasonable substrate for HLADH. Their rates of reduction relative to that of the usual cyclohexanone standard are recorded in Table I.

The racemic oxa and thia ketone substrates (±)-**1–3** were each subjected to preparative-scale HLADH-catalyzed reduction using ethanol to effect coupled-substrate recycling[6a,7] of the catalytic amount of nicotinamide coenzyme used. Each reaction was terminated when GLC analysis showed it to be ≤50% complete. The unchanged ketones and product alcohols were easily separated by chromatography. Their structures were then confirmed by comparisons with the racemic standards prepared above. The results are summarized in Table II.

The enantiomeric excesses of the recovered ketones (+)-**1**, (−)-**2**, and (+)-**3** were determined by their quantitative conversions to the corresponding ketals **10** and **11** with (−)-(2*R*,3*R*)-2,3-butanediol followed by ^{13}C NMR analysis.[8] The diastereomeric ketals obtained from the racemic ketones were used as reference standards. The ΔΔδ values observed for the diastereotopic carbon atoms for the ketals from (±)-**1–3** are recorded in Table III. The ee's of the product alcohols (+)-**4**, (1*R*,3*R*,6*S*)-**5**, (−)-**2**, and (+)-**7** were determined by ^1H NMR analysis of their Mosher esters in the presence of Eu(fod)$_3$.[9] The ΔΔδ values of the methoxy protons of the corresponding Mosher esters of the racemic alcohols used as the reference standards are recorded in Table IV. The de value for (+)-**9**-MTPA was confirmed by capillary GLC analysis.

Scheme II[a]

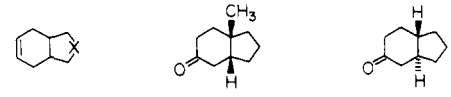


[a] (i) Raney nickel; (ii) CrO_3.

The relative C-3 configurations of the enzyme-derived alcohol products **4**, **5**, **7**, and **9** were established by literature correlations[10a] for **4** and **5** and by ^1H NMR assignment[10b,11] of C-3 axial or equatorial hydroxyl for **7** and **9**. The absolute configurations of the oxa series alcohols were assigned by their oxidation to the corresponding ketones ((+)-**4** and **5** → (−)-**1**, (+)-**7** → (+)-**2**) followed by octant rule[12] analyses of the Cotton effects observed in the ketone circular dichroism spectra. The absolute configurations of the recovered ketones (+)-**1** and (−)-**2** were also assigned from circular dichroism spectral analysis. In the thia series, the absolute configurations were established by conversions to *trans*-3,4-dimethylcyclohexanone (**12**) as shown in Scheme II, followed by octant rule[12] analyses of the CD spectra of (+)- and (−)-**12**.[13]

Discussion

The literature routes[10a,14,15] to (±)-**1,2** which involve epoxidation of an alkene precursor, **13**, X = O, of the desired cis or trans ring junction stereochemistry, proceeded smoothly. Regrettably, the sensitivity of sulfur to epoxidation conditions precluded the preparation of (±)-**3** from the corresponding cis[15] or trans junction thia alkene **13**, X = S, and the Scheme I route was used instead.



The 3β and 3α alcohols (±)-**4–7** required as reference compounds were intermediates in the syntheses of the substrate ketones (±)-**1,2**. Their C-3 configurations were assigned from their characteristic 3–5 ppm ^1H NMR signals. For the trans series alcohols (±)-**6,7**, the diagnostically critical C-3 proton resonances coincided with those of C-7 and C-9, and the C-3 stereochemical assignments[10b] were confirmed by examination[11] of the unobstructed C-3 proton resonances of their Mosher esters, (±)-**6**-MTPA and (±)-**7**-MTPA, respectively. The corresponding C-3 epimer assignments for the thia alcohols (±)-**8,9** were unambiguous, with the axial and equatorial proton resonances being clearly distinguishable.[11]

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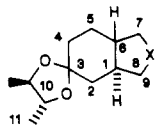
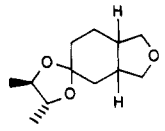
Table III. Chemical Shift Differences in the ^{13}C NMR Spectra of the Diastereomeric Ketals of (±)-1–3[a]

ketal		ppm C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-9	C-10[b]	C-11[c]
 10	X = O	0.03	1.80[d]	0	1.95[d]	0.37	0.51[d]	0	0	0.13	0.15
	X = S	0	0.93[d]	0	0.60[d]	0.38	0.46	0	0	0.28[d]	0.15
 11		0.07	0.14	0.07	0.48[d]	0.04	0.11	0.09	0.08	0.15	0.08

[a] From ^1H noise-decoupled NMR spectrum determined in C^2HCl_3. [b] Or C-10a. [c] Or C-11a. [d] Used for determination of ee values recorded in Table II.

Table IV. Enantiomeric Shift Differences for the Methoxyl Protons of the Diastereomeric Mosher Esters of (±)-4,5,7,9[a]

Mosher ester	$Eu(fod)_3$ (equiv)	(ppm)
(±)-4-MTPA	0.89	0.23
(±)-5-MTPA	0.97	0.38
(±)-6-MTPA	1.19	0.13
(±)-7-MTPA	1.05	0.15
(±)-9-MTPA	0.10	0.16

[a] Determined at 80 MHz in CCl_4.

Each of the ketones (±)-1–3 was a reasonable HLADH substrate, and the preparative-scale reactions proceeded normally with good recoveries of products.[16] For the trans series, reduction of both the oxa and thia ketones was highly enantiomerically selective and diastereotopically specific for the pro-*R* faces of the carbonyl groups of the 1*R*,6*R* stereoisomers of **2** and **3**. The low ee of the recovered ketones reflects the incomplete extent of reaction.[17] While highly 1*R*,6*S* enantioselective and diastereotopic pro-*R* carbonyl face reduction of the 1*R*,6*S* enantiomer to give (+)-**4** is highly favored with the cis oxa ketone (±)-**1** as substrate, some reduction of both enantiomers to **5** also occurs, with the low ee of the recovered ketone (+)-**1** reflecting this situation.

The ee and absolute configuration determinations were straightforward. Octant rule analyses of the Cotton effects of the CD spectra of the oxa ketones (+)- and (−)-**1** and **2** were unequivocal and agreed with those of the ORD data of their close analogues (−)-**14**[18] and (+)-**15**,[19] respectively, thereby confirming that the oxygen substituents of **1** and **2** are too remote to distort unduly the CD of the carbonyl absorptions. The thia ketones (+)- and (−)-**3** could not be analyzed similarly because of double Cotton effects, one positive and one negative, in each CD spectrum.[20] However, this problem was quickly resolved by the Scheme II degradations to (+)- or (−)-**12** prior to octant rule analyses.

The courses of the HLADH-catalyzed reduction of the oxa and thia substrates of this study parallel those observed with their carbobicyclic analogues.[22] The results confirm the conclusions drawn for monocyclic substrates, that oxygen- and sulfur-containing substrates are well-tolerated by HLADH and do not alter the stereospecificity of the enzymic catalysis. The enantiomeric and diastereotopic selectivities observed in the Table II transformations are fully in accord with the predictions of the cubic HLADH active-site section model, with the enzyme–substrate binding analyses being identical with those described[22] for the analogous *cis*- and *trans*-decalone substrates.

Experimental Section

The instrumentation, general purification, and analytical procedures used, and enzyme and coenzyme sources, were as described previously,[6b] except that capillary GLC analyses were performed on a Varian Aerograph 2740-10 instrument equipped with a 30 m × 0.25 mm column of DB-1 0.25 μm coated fused silica gel. Preparative GLC was carried out with 6 m × 1 cm 5% Carbowax or 3 m × 1 cm 10% Dowfax on Chromosorb GHP columns. Boiling points are for Kugelrohr distillations. Unless noted otherwise, IR spectra are for films and ^1H NMR data for $CDCl_3$ solutions.

Preparations of Substrates (±)-1–3 and Reference Alcohols (±)-4–9. Cis Ring Junction, Oxa Series. 3,4-Epoxy-*cis*-8-oxabicyclo[4.3.0]nonane, prepared from *cis*-1,2,3,6-tetrahydrophthalic anhydride[14] by the literature[10a,15] procedures, was reduced with $LiAlH_4$[10a] to give >90% yields of mixtures of the alcohols (±)-**4** and (±)-**5** (14:86 ratio with 1.4 molar equiv of $LiAlH_4$ and 75:25 with 6-fold molar excess of $LiAlH_4$). These were purified by preparative GLC (Carbowax) to give *cis*-8-oxabicyclo[4.3.0]-nonan-3β-ol ((±)-**4**) [bp 120 °C (10 mmHg) (lit.[10a] bp 115 °C (9 mmHg)); IR 3430 cm^{-1}; ^1H NMR δ 1.00–2.70 (m, 9 H) and 3.40–4.10 (m, 5 H)] and *cis*-8-oxabicyclo[4.3.0]nonan-3α-ol ((±)-**5**) [bp 120 °C (10 mmHg) (lit.[10a] bp 115 °C (9 mmHg)); IR 3410 cm^{-1}; ^1H NMR δ 1.10–2.50 (m, 9 H) and 3.40–4.00 (m, 5 H).

Oxidation of a mixture of (±)-**4**,**5** (75:25, 5.68 g, 40 mmol) in CH_2Cl_2 (50 mL) with chromium trioxide (24 g, 240 mmol) in dry pyridine (38 g, 480 mmol) and CH_2Cl_2 (400 mL) by the literature[10a] procedure gave *cis*-8-oxabicyclo[4.3.0]nonan-3-one ((±)-**1**, 4.1 g, (73% yield): bp 118–120 °C (19 mmHg)); IR 1715 cm^{-1}; ^1H NMR δ 1.50–2.90 (m, 8 H) and 3.40–4.20 (m, 4 H).

Trans Junction, Oxa Series. 3,4-Epoxy-*trans*-8-oxabicyclo[4.3.0]nonane,[10b] prepared from *trans*-8-oxabicyclo[4.3.0]non-3-ene[10a] by the literature[10b] method, was reduced with $LiAlH_4$[10b] to give quantitative yields of mixtures of the alcohols (±)-**6** and (±)-**7** (94:6 ratio with 1.25 molar equiv of $LiAlH_4$ and 15:85 with 6-fold molar excess of $LiAlH_4$). These were purified by preparative GLC (Dowfax) to give *trans*-8-oxabicyclo[4.3.0]nonan-3β-ol ((±)-**6**) [bp 118–120 °C (10 mmHg)); IR 3360 cm^{-1}; ^1H NMR δ 0.80–2.40 (m, 9 H) and 3.1–4.20 (m, 5 H)] and *trans*-8-oxabicyclo[4.3.0]-

(16) The low yields of (+)-**4** and **5** (Table II) are the result of their purification by GLC.

(17) We discovered subsequently that our GLC-based monitoring of the HLADH-catalyzed reactions overestimated the percentage of reduction.

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nonan-3α-ol ((±)-7) [bp 115 °C (9 mmHg) (lit.[10b] bp 120 °C (10 mmHg)); IR 3380 cm^{-1}; ^1H NMR δ 1.00–2.60 (m, 9 H) and 3.15–3.60 (m, 2 H).

Oxidation of a mixture of (±)-6,7 (15:85, 5.68 g, 40 mmol) with chromium trioxide–pyridine as above[10] gave *trans*-8-oxabicyclo-[4.3.0]nonan-3-one ((±)-2, 4.3 g, 77% yield): bp 120 °C (18 mmHg) (lit.[10b] bp 120–121 °C (18 mmHg)); IR 1715 cm^{-1}; ^1H NMR δ 1.00–2.80 (m, 8 H), 3.10–3.60 (m, 2 H), and 3.80–4.20 (m, 2 H).

Thia Series. *trans*-8-Thiabicyclo[4.3.0]nonan-3-one ((±)-3). Diethyl *trans*-4-oxocyclohexane-1,2-dicarboxylate (13.4 g, 54.6 mmol, prepared by the method of Jung and McCoombs[23]), triethyl orthoformate (8.9g, 60 mmol) and *p*-toluenesulfonic acid (0.1 g) in dry EtOH (90 mL) was stirred at 20 °C for 18 h. The ethanol was then rotoevaporated and the residue dissolved in diethyl ether (100 mL). The ether solution was washed with saturated aqueous $NaHCO_3$ (3 × 25 mL) and then with water (25 mL), dried ($MgSO_4$), and then rotoevaporated and Kugelrohr-distilled to give diethyl *trans*-4,4-diethoxycyclohexane-1,2-dicarboxylate (14.3 g, 83% yield): bp 87–90 °C (0.08 mmHg); IR 1735 cm^{-1}; ^1H NMR δ 1.20 (m, 12 H), 1.40–3.10 (m, 8 H), 3.43 (dq, 4 H) and 4.10 (q, 4 H); ^{13}C NMR 13.60, 14.77, 14.95, 24.88, 31.96, 35.26, 41.58, 43.85, 54.51, 54.79, 59.82 (2 C), 98.24, 173.58, and 173.68 ppm.

This diethoxy ketal (14.1 g, 41.4 mmol) in THF (60 mL) was added dropwise at 20 °C with stirring to $LiAlH_4$ (2.2 g, 58.3 mmol) in THF (60 mL). The mixture was refluxed for 1 day and then cooled to 20 °C, and saturated aqueous sodium potassium tartrate (Rochelle salt) was added dropwise until a white precipitate appeared. The mixture was then refluxed again for 4 h, cooled, filtered, rotary evaporated, and finally Kugelrohr distilled to give *trans*-4,4-diethoxy-1,2-bis(hydroxymethyl)cyclohexane (8.5 g, 82% yield), bp 100 °C (0.04 mmHg), recrystallized from ethyl acetate–hexane: mp 75–75.5 °C; IR 3360 cm^{-1}; ^1H NMR δ 1.17 (t, 6 H), 1.0–2.3 (m, 8 H), and 3.2–3.9 (m, 10 H, 8 H after D_2O addition); ^{13}C NMR 15.07, 15.23, 25.89, 32.61, 36.51, 40.42, 43.17, 54.69, 54.86, 66.13 (2 C), and 99.84 ppm. Anal. Calcd for $C_{12}H_{20}O_4$: C, 62.04; H, 10.41. Found: C, 62.14; H, 10.58.

The above diol (8.5 g, 36.6 mmol) in dry pyridine (50 mL) was added dropwise at 0 °C to a stirred solution of *p*-toluenesulfonyl chloride (20.65 g, 108 mmol) in pyridine (100 mL). The mixture was stirred at 0 °C for 2 h and then kept at 4 °C for 1 day. Water (150 mL) was then added, the mixture was extracted with diethyl ether (3 × 100 mL), and the ether solution was washed successively with water (4 × 100 mL), cold (0 °C) 1 M hydrochloric acid (2 × 100 mL), saturated aqueous $NaHCO_3$ (100 mL), and water (100 mL) and then dried ($MgSO_4$). Rotoevaporation afforded the bis-*p*-toluenesulfonate (17.5 g, 88% yield): mp 50–58 °C; ^1H NMR δ 1.13 (t, 6 H), 1.0–2.5 (m, 8 H), 2.46 (s, 6 H), 3.40 (m, 4 H), 3.93 (br s, 4 H), and 7.35 (dd, 8 H).

This material (5.5 g, 10.2 mmol, used without further purification) and Na_2S (7.5 g, 96 mmol) in 50% aqueous EtOH (125 mL) was heated under reflux for 4 h and then cooled to 20 °C. Hydrochloric acid (2 M, 150 mL) was then added and the mixture was stirred for 1.5 h, then filtered, and extracted with diethyl ether (3 × 100 mL). The ether solution was washed with 5% aqueous $NaHCO_3$ (2 × 100 mL) and then with water (100 mL), dried ($MgSO_4$), and rotoevaporated. Recrystallization of the solid obtained from CH_2Cl_2–pentane gave *trans*-8-thiabicyclo[4.3.0]-nonan-3-one ((±)-3, 1.15 g, 72% yield): mp 74.5–75.0 °C; IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR δ 1.00–3.17 (m, 12 H); ^{13}C NMR 28.35, 34.86, 36.04, 39.02, 45.87, 46.37, 48.55, and 209.11 ppm. Anal. Calcd for $C_8H_{12}OS$: C, 61.50; H, 7.74; S, 20.52. Found: C, 61.71; H,7.76; S, 20.71.

***trans*-8-Thiabicyclo[3.3.0]nonan-3β-ol ((±)-8).** *trans*-8-Thiabicyclo[4.3.0]nonan-3-one ((±)-3, 220 mg, 1.41 mmol) in dry THF (15 mL) was reduced with $LiAlH_4$ (100 mg, 2.63 mmol) in dry THF (35 mL) to give, after flash chromatography and recrystallization from ethyl acetate–hexane, *trans*-8-thiabicyclo-[4.3.0]nonan-3β-ol ((±)-8, 134 mg, 60% yield): mp 95 °C; IR 3400 cm^{-1}; ^1H NMR δ 1.00–3.10 (m, 13 H (including OH)) and 3.67 (br s, axial H); ^{13}C NMR 28.18, 34.81, 35.77, 35.95, 40.19, 47.27, 47.70, and 70.53 ppm. Anal. Calcd for $C_8H_{14}OS$: C, 60.71; H, 8.92; S, 20.26. Found: C, 60.96; H, 9.13; S, 19.95.

***trans*-8-Thiabicyclo[4.3.0]nonan-3α-ol ((±)-9).** The above 3β alcohol ((±)-8, 100 mg, 0.63 mmol), triphenylphosphine (331 mg, 1.26 mmol), and benzoic acid (154 mg, 1.26 mmol) in THF (10 mL) were stirred at 20 °C and diethyl azadicarboxylate (220 mg, 1.26 mmol) in THF (1.5 mL) added dropwise.[24] Stirring was continued for 14 h and the solvent then rotoevaporated. The residue was flash chromatographed to give 3α-(benzoyloxy)-*trans*-8-thiabicyclo[4.3.0]nonane (139 mg, 83% yield): mp 70–71 °C; IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR δ 1.10–3.10 (m, 12 H), 5.40 (s, equatorial H), and 7.40–8.30 (m, 5 H). This material (56 mg, 0.21 mmol) was hydrolyzed with 50% aqueous $Ba(OH)_2$ (2 M, 50 mL) at reflux for 2 h to give, after recrystallization from ethyl acetate–hexane, *trans*-8-thiabicyclo[4.3.0]nonan-3α-ol ((±)-9, 27 mg, 79% yield): mp 53–54 °C; IR ($CHCl_3$) 3350 cm^{-1}; ^1H NMR δ 1.20–3.10 (m, 13 H (including OH)), and 4.17 (s, equatorial H); ^{13}C NMR 25.46, 32.48, 36.75, 38.17, 41.81, 48.16, and 66.12 ppm. Anal. Calcd for $C_8H_{14}OS$: C, 60.71; H, 8.92; S, 20.26. Found: C, 60.36; H, 8.70; S, 20.49.

***trans*-8-Thiabicyclo[4.3.0]non-3-ene (13, X = S).** *trans*-1,2-Bis(hydroxymethyl)cyclohex-4-ene[15] (21.8 g, 152 mmol) in pyridine (30 mL) was reacted at 0 °C with *p*-toluenesulfonyl chloride (87 g, 576 mmol) in pyridine (60 mL) to give, after recrystallization from MeOH, the bis-tosylate derivative (60 g, 82% yield): mp 94.5–95.5 °C; ^1H NMR δ 2.00 (br s, 6 H), 2.50 (s, 6 H), 4.00 (d, 4 H), 5.58 (d, 2 H), and 7.60 (dd, 8 H). This compound (21.5 g, 48 mmol) and sodium sulfide (15.6 g, 65 mmol) in 95% aqueous EtOH (250 mL) was refluxed for 3 days, and the EtOH was then removed by rotoevaporation. Water (200 mL) was added and the mixture extracted with diethyl ether (2 × 100 mL). The ether solution was washed with water (50 mL), dried ($MgSO_4$), and rotoevaporated, and the residue was recrystallized from EtOH to give *trans*-8-thiabicyclo[4.3.0]non-3-ene (13, X = S, 4.0 g, 60% yield): mp 77–78 °C; IR ($CHCl_3$) 1660 cm^{-1}; ^1H NMR δ 1.50–2.73 (m, 8 H), 3.10 (m, 2 H), and 5.63 (d, 2 H); ^{13}C NMR 31.23, 36.63, 43.68 and 180.48 ppm. Anal. Calcd for $C_8H_{12}S$: C, 68.51; H, 8.62; S, 22.86. Found: C, 68.45; H, 8.43; S, 22.66.

Relative Rates of HLADH-Catalyzed Reductions of (±)-1–3. The assays were carried out as described previously[6a] on solutions 2×10^{-2} M in (±)-1,2 and 10^{-3} M in (±)-3. The results are summarized in Table I.

Preparative-Scale HLADH-Catalyzed Reductions of (±)-1–3. All reductions were carried out by the general procedure reported previously[6a] except that chromatographic purifications on silica gel were effected with benzene/ether (1:1) for the oxa series substrates and with ethyl acetate/hexane (2:3) for the thia compounds. The results for the individual reactions are given below (cf. Table II). For each reaction, the IR and ^1H NMR spectral data were identical with those recorded above for the corresponding racemates.

Reduction of (±)-1 (1.0 g, 7.1 mmol) for 5 days (44% transformation by GLC) yielded (+)-(1*S*,6*R*)-1 (507 mg, 51% yield, 52% ee) [bp 118–120 °C (19 mmHg) (lit.[10a] bp (±) 118–119 °C (19 mmHg)); $[\alpha]^{25}_D$ +43.8° (*c* 1, $CHCl_3$)] and a mixture of 4 and 5, separated by preparative-scale GLC (Dowfax): (+)-(1*R*,3*S*,6*S*)-4 (165 mg, 17% yield, 93% ee) [bp 120–122 °C (10 mmHg) (lit.[10a] bp (±) 115 °C (9 mmHg)); $[\alpha]^{25}_D$ +3.7° (*c* 3.2, EtOH)] and (1*R*,3*R*,6*S*)-5 (50 mg, 5% yield, 19% ee) [bp 120–122 °C (10 mmHg) (lit.[10a] bp (±) 115 °C (9 mmHg)); $[\alpha]^{25}_D$ 0° (*c* 0.9, EtOH or $CHCl_3$).

Reduction of (±)-2 (1.0g, 7.1 mmol) for 2 days (40% transformation by GLC) afforded (−)-(1*S*,6*S*)-2 (477 mg, 48% yield, 60% ee) [bp 120–122 °C (18 mmHg) (lit.[10b] bp (±) 120–122 °C (18 mmHg)); $[\alpha]^{25}_D$ −9.1° (*c* 1, EtOH)] and (+)-(1*R*,3*S*,6*R*)-7 (262 mg, 26% yield, >97% ee) [bp 122–124 °C (10 mmHg) (lit.[10b] bp (±) 120 °C (10 mmHg)); $[\alpha]^{25}_D$ +54.4° (*c* 1, $CHCl_3$)].

Reduction of (±)-3 (505 mg, 3.24 mmol) for 5 days (50% transformation by GLC) gave (+)-(1*S*, 6*S*)-3 (265 mg, 52% yield, 53% ee) [mp 68.5–69.5 °C; $[\alpha]^{25}_D$ +15.6° (*c* 1, EtOH)] and (+)-(1*R*,3*S*,6*R*)-9 (168 mg, 33% yield, >97% ee) [mp 70.0–70.5 °C; $[\alpha]^{25}_D$ +40.0° (*c* 1, EtOH)].

Enantiomeric Excess Determinations of 1–3 Recovered from HLADH-Catalyzed Reductions. The optically active ketones (+)-1, (−)-2, and (+)-3, and their racemic counterparts

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as reference standards, were converted to the corresponding ketals **10**, X = O,S, and **11** with (−)-(2*R*,3*R*)-2,3-butanediol by the general procedure described earlier.[6a] The ^{1}H-decoupled ^{13}C NMR spectrum of each was recorded. The ee values of the ketals of optically active **1–3** were then determined[8] by direct measurement of the signal intensities of the selected diastereotopic carbon atoms whose enantiomeric shift differences are identified in Table III. The ee values are recorded in Table II. The ^{13}C NMR data for the racemic ketals are as follows.

(+)-1-ketal (11): bp 132–134 °C (18 mmHg); ^{13}C NMR 16.91 and 16.99 (C-11), 22.04 and 22.08 (C-5), 31.89 and 32.37 (C-4), 35.76 and 35.90 (C-2), 36.69 and 36.80 (C-6), 38.05 and 38.12 (C-1), 70.14 and 70.23 (C-7), 73.00 and 73.08 (C-9), 77.97 and 78.12 (C-10), and 107.82 and 107.89 (C-3) ppm.

(+)-2-ketal (10, X = O): bp 130–132 °C (18 mmHg); ^{13}C NMR 16.82 and 16.97 (C-11), 23.80 and 24.17 (C-5), 35.83 and 37.78 (C-4), 37.03 and 38.83 (C-2), 43.17 and 43.68 (C-6), 44.87 and 44.90 (C-1), 71.60 and 71.69 (C-7, C-9), 78.10 and 71.23 (C-10), and 108.46 (C-3) ppm.

(±)-3-ketal (10, X = S): bp 80 °C (0.3 mmHg); ^{13}C NMR 16.81 and 16.96 (C-11,11a), 27.13 and 27.51 (C-5), 35.27 and 35.87 (C-6), 47.50 (C-1), 77.94 and 77.82 (C-10a), 78.59 (C-10) and 108.29 (C-3) ppm.

Enantiomeric Excess Determinations of the 4, 5, 7, and 9 Products of HLADH-Catalyzed Reductions. The optically active alcohols (+)-**4**,**5**, (+)-**7**, and (+)-**9**, and their reference standard racemates, were converted into their MTPA esters as described previously[6b] and the $\Delta\Delta\delta$ values (Table IV) of their methyl protons monitored by 80-MHz ^{1}H NMR spectroscopy in the presence of Eu(fod)$_3$.[9] The ee values are summarized in Table II. For (+)-**9**-MTPA, the NMR-derived de was confirmed by capillary GLC analysis. The C-3 proton regions of the MTPA esters were used to corroborate the axial or equatorial proton assignments[11] of the parent alcohols. The ^{1}H NMR spectral data (in CCl_4) for the "racemate" esters are as follows.

(±)-4-MTPA δ 1.00–2.00 (m, 6 H), 2.00–2.70 (m, 2 H), 3.40–4.00 (m, 4 H), 3.50–3.60 (app d, 3 H, OMe), 5.00–5.50 (m, 1 H), and 7.30–7.70 (m, 5 H).

(±)-5-MTPA δ 1.00–2.00 (m, 6 H), 2.00–2.60 (m, 2 H), 3.40–4.00 (m, 4 H), 3.50–3.60 (app d, 3 H, OMe), 4.70–5.30 (m, 1 H), and 7.30–7.70 (m, 5 H).

(±)-6-MTPA δ 1.00–2.50 (m, 8 H), 3.00–3.50 (m, 2 H), 3.80–4.20 (m, 2 H), 3.50–3.60 (app d, 3 H, OMe), 4.80–5.50 (m, 1 H), and 7.30–7.80 (m, 5 H).

(±)-7-MTPA δ 1.10–2.80 (m, 8 H), 3.00–3.50 (m, 2 H), 3.70–4.20 (m, 2 H), 3.50–3.70 (app d, 3 H, OMe), 5.30–5.50 (m, 1 H), and 7.30–7.60 (m, 5 H).

(±)-9-MTPA δ 0.90–3.00 (m, 12 H), 3.48 (s, 3 H, OMe), 5.30 (s, C-3 equatorial H), 7.36 (br s, 5 H).

Relative Configuration Determinations. The C-3 configurational assignments for (+)-**4** and (1*R*,3*S*,6*S*)-**5** were made from the literature correlations[10a] of their racemates and from the characteristic axial or equatorial C-3 ^{1}H NMR patterns[10b,11] for (+)-**7** and (+)-**9**.

Absolute Configuration Determinations. The enzyme-derived oxa alcohols (+)-**4**,**5** and (+)-**7** were oxidized as outlined previously[6b] with pyridinium chlorochromate to give the corresponding ketones (−)-**1** and (+)-**2**. The absolute configurations of these ketones, and of (+)-**1** and (−)-**2**, recovered from the HLADH-catalyzed reactions, were determined by octant rule[12] analysis of their CD spectra determined at 20 °C for 0.004 M solutions in EtOH. These are recorded below.

(−)-**1** (from (+)-**4**): CD $[\Theta]_{336}$ 0°, $[\Theta]_{289}$ −5300°, $[\Theta]_{230}$ 0°.
(−)-**1** (from **5**): CD $[\Theta]_{336}$ 0°, $[\Theta]_{288}$ −240°, $[\Theta]_{240}$ 0°.
(+)-**2** (from (+)-**7**): CD $[\Theta]_{335}$ 0°, $[\Theta]_{289}$ −1825°, $[\Theta]_{233}$ 0°.
(+)-**1** (recovered): CD $[\Theta]_{336}$ 0°, $[\Theta]_{289}$ +2588°, $[\Theta]_{231}$ 0°.
(−)-**2** (recovered): CD $[\Theta]_{335}$ 0°, $[\Theta]_{291}$ +1438°, $[\Theta]_{234}$ 0°.

Absolution Configuration of (+)-3. (+)-*trans*-8-Thiabicyclo[4.3.0]nonan-3-one ((+)-**3**, 53 mg, 0.34 mmol) was desulfurized with Raney Ni (2 g) in diethyl ether (25 mL) to give a 1:1 mixture of *trans*-3,4-dimethylcyclohexan-1α- and -1β-ol (20 mg, 46% yield): bp 70 °C (100 mmHg); IR 3360 cm^{-1}; ^{1}H NMR δ 0.60–2.20 (m, 9 H (including OH)), 0.93 (br s, 6 H), 3.5 (br s, $^1/_2$H) and 6.05 (br s, $^1/_2$H). This dimethylcyclohexanol (19 mg, 0.015 mmol) was oxidized at 20 °C for 17 h with Jones reagent to afford (3*S*,4*S*)-3,4-dimethylcyclohexanone ((±)-**12**, 15.6 mg, 80% yield): IR 1720 cm^{-1}; ^{1}H NMR δ 0.63–2.56 (m, 8 H) and 1.00 (d, 6 H); CD (*c* 0.0042 M, EtOH, 20 °C) $[\Theta]_{325}$ 0°; $[\Theta]_{288}$ +33.3°; $[\Theta]_{240}$ 0°.

Absolute Configuration of (+)-9. (+)-*trans*-8-Thiabicyclo[4.3.0]nonan-3α-ol ((+)-**9**, 23.5 mg, 0.15 mmol) was desulfurized with Raney Ni (2 g) in MeOH (20 mL) under reflux for 20 min to give *trans*-3,4-dimethylcyclohexan-3α-ol (12 mg, 63% yield): bp 75–80 °C (100 mmHg); IR 3360 cm^{-1}; ^{1}H NMR δ 0.73–2.23 (m, 9 H, including OH), 0.91 (br s, 6 H) and 4.05 (s, 1 H). This material (12 mg, 0.0094 mmol) was oxidized at 20 °C for 17 h with Jones reagent to give (3*R*,4*R*)-3,4-dimethylcyclohexanone ((−)-**12**, 11.2 mg, 94% yield); IR 1720 cm^{-1}; ^{1}H NMR δ 0.63–2.56 (m, 8 H) and 1.00 (d, 6 H); CD (*c* 0.0089 M, EtOH, 20 °C) $[\Theta]_{328}$ 0°, $[\Theta]_{290}$ −47.25°, $[\Theta]_{235}$ 0° (lit.[25] ORD $[\phi]_{589}^{22}$ −37.21°, $[\phi]_{400}^{22}$ −120.93°, $[\phi]_{350}^{22}$ −241.86°, $[\phi]_{306}^{22}$ −930.23°, $[\phi]_{289}^{22}$ 0°, $[\phi]_{267}^{22}$ +893.02°, $[\phi]_{260}^{22}$ +251.16°).

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Registry No. (±)-**1**, 113251-25-5; (−)-**1**, 113348-80-4; (+)-**1**, 113348-81-5; (±)-**2**, 113251-26-6; (+)-**2**, 113348-82-6; (−)-**2**, 113348-83-7; (±)-**3**, 113251-27-7; (+)-**3**, 113348-84-8; (±)-**4**, 113251-28-8; (+)-**4**, 113348-85-9; (±)-**4**-MTPA, 113251-36-8; **5**, 113348-86-0; (±)-**5**, 113251-29-9; (±)-**6**, 113251-30-2; (±)-**7**, 113251-31-3; (+)-**7**, 113348-87-1; (±)-**8**, 113251-32-4; (±)-**9**, 113348-77-9; (+)-**9**, 113348-88-2; (±)-**9**-MTPA, 113251-37-9; **10** (X = O), 113251-33-5; **10** (X = S), 113251-34-6; (−)-**12**, 69127-34-0; (+)-**12**, 113348-79-1; **13** (X = S), 113251-35-7; 3,4-epoxy-8-oxabicyclo[4.3.0]nonane, 42996-49-6; *cis*-1,2,3,6-tetrahydrophthalic anhydride, 935-79-5; *trans*-8-oxabicyclo[4.3.0]non-3-ene, 56000-18-1; diethyl *trans*-4-oxocyclohexane-1,2-dicarboxylate, 113251-38-0; *trans*-4,4-diethoxycyclohexane-1,2-dicarboxylate, 113273-57-7; *trans*-4,4-diethoxy-1,2-bis(hydroxymethyl)cyclohexane, 113251-39-1; trans-4,4-diethoxy-1,2-bis(hydroxymethyl)cyclohexane bis(toluenesulfonate), 113251-40-4; 3α-(benzyloxy)-*trans*-8-thiabicyclo[4.3.0]nonane, 113251-41-5; *trans*-1,2-bis(hydroxymethyl)cyclohex-4-ene, 13149-04-7; *trans*-1,2-bis(hydroxymethyl)cyclohex-4-ene bis(tosylate), 20518-14-3; (−)-(2*R*,3*R*)-2,3-butanediol, 24347-58-8; *trans*-3,4-dimethylcyclohexan-1α-ol, 69308-17-4; *trans*-3,4-dimethylcyclohexan-1β-ol, 69127-36-2.

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