Enzymes in Organic Synthesis. 27.[1] Horse Liver Alcohol Dehydrogenase Catalyzed Oxidoreductions of 3-Alkylthiopyran Ketones and Alcohols

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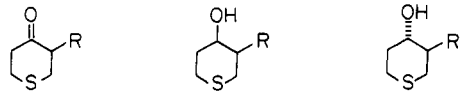
The stereospecificity of horse liver alcohol dehydrogenase (HLADH) toward S-heterocyclic substrates has been studied further. While 3-methyl- and 3-ethyltetrahydrothiopyran-4-ones (1) and -4-ols (2, 3) are not good substrates, the ketones 1 and trans alcohols 3 do undergo highly stereoselective enzyme-mediated oxidoreductions in preparative-scale (up to 2 g of substrate) reactions. In contrast, HLADH-catalyzed oxidations of the cis alcohols 2 are too slow to be preparatively viable. Reductions of the racemic ketones 1 occur with high enantiomeric- and stereoselectivity, with the 3*S* enantiomers being converted in excellent yields to the corresponding 3*S*,4*S* trans alcohols 3 of 78–90% ee. The unreactive 3*R* ketone enantiomers of 58–66% ee are recovered from the same reactions. Oxidations of the racemic trans alcohols 3 are also markedly stereoselective, permitting the unreactive (3*R*,4*R*)-3 enantiomers of 65–85% ee to be isolated in good yields.

The asymmetric synthetic opportunities provided by the use of enzymes as chiral catalysts are well documented.[2] Horse liver alcohol dehydrogenase (HLADH[3]), a nicotinamide coenzyme-dependent enzyme that catalyzes stereospecific C=O ⇌ CH(OH) interconversions of a broad structural range of alcohol and ketone substrates, is one of the most versatile enzymes in this regard.[1,2a,b,l-q] To date, substrates containing heteroatoms have received relatively little attention.[4,5] Accordingly, prompted by the synthetic value of chiral heteroatom-containing compounds, we began a survey of HLADH-catalyzed oxidoreductions of heterocyclic alcohols and ketones in order to evaluate the influences of heteroatoms on the specificity of the enzyme. The initial work on 2-substituted tetrahydropyran and -thiopyran substrates showed that such enzyme-catalyzed transformations largely paralleled those of their 3-alkylcyclohexane carbocyclic analogues[2a,6,7] and were extremely stereoselective, giving products of very high enantiomeric excess (ee) in excellent yields.[4] In view of the enantiomeric discrimination differences between 2-alkyl and 3-alkylcyclohexanone substrates,[2a,6,7] the study has now been extended to the 3-alkyltetrahydrothiopyran ketones and alcohols **1–3a,b**. The results obtained again



a, R = Me
b, R = Et

reflect those for the carbocyclic analogues and demonstrate that preparative-scale HLADH-catalyzed oxidoreductions of the S-containing substrates are also highly stereo- and enantioselective. The enzymic approach provides a convenient and practical route of asymmetric synthetic value to optically active thiopyranones 1 and trans alcohols 3 of high enantiomeric excesses.

Results

Preparation of Substrates. The racemic substrates **1–3a,b** were prepared as outlined in Scheme I. The common intermediate, the potassium salt of 3-carbomethoxytetrahydrothiopyran-4-one (**5**), was obtained in 54% overall yield from methyl acrylate, and the ketones

Scheme I

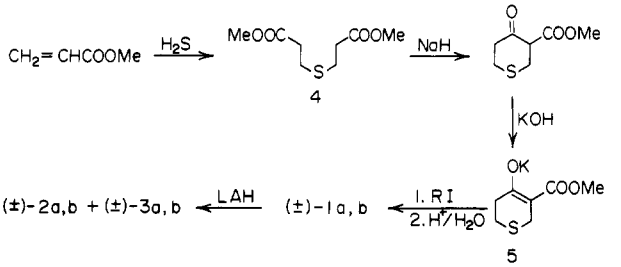


Table I. Relative Rates[a] of HLADH-Catalyzed Oxidoreductions of (±)-1-3a,b

reduction		oxidation	
substrate	rel rate	substrate	rel rate
cyclohexanone	100	cyclohexanol	100
(±)-1a	1.0	(±)-2a	3.6
(±)-1b	1.0	(±)-2b	1.3
		(±)-3a	4.8
		(±)-3b	5.0

[a] Measured spectrophotometrically at 25 °C in 0.1 M phosphate buffer (pH 7) for reduction and in 0.05 M glycine-NaOH buffer (pH 9) for oxidation.

(±)-**1a** and (±)-**1b** were prepared in 46% and 72% yields, respectively, from **5**. The lithium aluminum hydride re-

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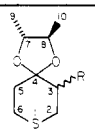
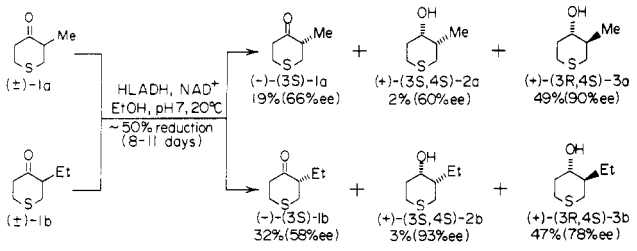
Table II. Enantiomeric Shift Differences in the ^{13}C NMR Spectra of the Diastereomeric Ketals 6a,b[a]

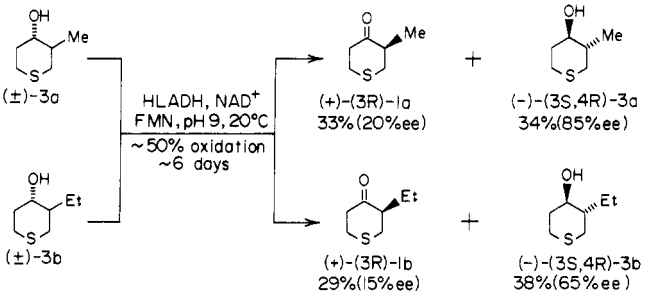
ketal structure	compd	Δδ,[c] ppm C-3	C-4	C-5	C-6	C-7	C-8	C-9	other C
 6	6a (R = Me)	0.75[b]	0	0.45[b]	0.11[b]	0.45[b]	0.28[b]	0.09	0.10 (CH_3)
	6b (R = Et)	0.58[b]	0.17[b]	0.20[b]	0.18[b]	0.13[b]	0	0.09	0 (CH_2CH_3), 0.13 (CH_2CH_3)

[a] ^1H noise-decoupled spectra determined in C^2HCl_3. [b] Used for evaluating the ee values of Schemes II and III. [c] A Δδ value of zero was obtained for C-2 and C-10 in both cases.

Scheme II



Scheme III

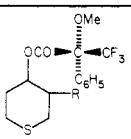
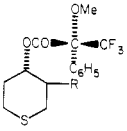


ductions of (±)-**1a,b** to ~1:1 mixtures of the cis and trans alcohols (±)-**2a,b** and (±)-**3a,b** were virtually quantitative. The cis–trans mixtures were separated into their individual components by MPLC and the individual stereoisomers identified by ^1H NMR spectroscopic comparisons of the chemical shifts and half-widths of the C-4 protons[8] of each cis–trans pair.

HLADH-Catalyzed Reductions of (±)-1a,b. The rates of HLADH-catalyzed reductions of (±)-**1a,b**, relative to that of the standard reference cyclohexanone, are recorded in Table I. While both racemates are poor substrates they were considered suitable candidates for preparative-scale work since their relative rates of reduction are comparable with the 0.9 value[6] of the carbocyclic analogue (±)-2-methylcyclohexanone for which preparative-scale HLADH-catalyzed reductions are well documented.[2a,6,7]

The synthetic-scale HLADH-mediated reductions of the thiopyranones (±)-**1a,b** were performed by using ethanol to effect coupled-substrate recycling of the catalytic amount of expensive nicotinamide coenzyme[2a,9] used. Each reaction was terminated when GLC analysis showed it to be ~50% complete. The products were isolated by chloroform extraction and separated by MPLC. The identities of the recovered ketones and product alcohols were confirmed by comparison with their racemic counterparts obtained from the Scheme I reactions. The results are summarized in Scheme II.

Table III. Enantiomeric Shift Differences for the Methoxyl Protons of the MTPA Esters of (±)-7a,b and (±)-8a,b[a]

structures	compd	$Eu(fod)_3$, equiv	ΔΔδ, ppm
 7	7a (R = Me)	0.23	0.34
	7b (R = Et)	0.19	0.70
 8	8a (R = Me)	0.64	1.32
	8b (R = Et)	1.05	1.50

[a] Determined at 60 MHz in CCl_4 solutions.

With cyclohexanol as the reference substrate, the relative rates of HLADH-catalyzed oxidations of the *cis*- and *trans*-thiopyranols **2a,b** and **3a,b**, respectively, are shown in Table I. Although the trans isomers are clearly better substrates than their cis analogues, none of the Table I alcohols is a good substrate. From the relative rate data, HLADH-promoted oxidations of the trans alcohols **3a,b** would be expected to be of marginal preparative viability. The velocities of the cis compounds **2a,b** are below the normal threshold levels for preparative-scale oxidations to be viable.[10] Nevertheless, each of the racemic *cis*- and *trans*-thiopyranols was subjected to a preparative-scale enzyme-catalyzed oxidation, with FMN as the recycling agent[11] for the catalytic NAD^+ employed. As expected, oxidations of the cis alcohols were not synthetically satisfactory. Even after up to 49-day reaction periods,

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

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(10) Usually preparative-scale HLADH-catalyzed oxidations can be performed successfully if the substrate is oxidized at a rate >10% that of cyclohexanol. For reductions, reactions are practical for most substrates with a reduction rate of >1% that of cyclohexanone.

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(±)-**2a,b** were oxidized to the extent of only 5–15%, and the reactions were not pursued further. In contrast, for the trans compounds (±)-**3a,b**, HLADH-catalyzed oxidation proceeded smoothly to reach the 50% oxidation point within 6 days. The reaction mixtures were worked up and the products identified as outlined above for the Scheme II reduction experiments. The oxidation results are summarized in Scheme III.

Enantiomeric Excess Determinations. The ee's of the optically active ketones **1a,b** of Schemes II and III were determined by their quantitative conversion to the corresponding ketals **6a,b** with (−)-(2*R*,3*R*)-2,3-butanediol, followed by ^{13}C NMR examinations[12] of the diastereomeric mixtures obtained. The ketals derived from the racemic ketones were used as reference standards. The ^{13}C signals were assigned by comparison with the 2-alkylthiopyranone[4a] and 2-alkylcyclohexanone[13] spectra. The $\Delta\delta$ values observed for the individual diastereotopic carbon atoms are recorded in Table II. The ee values of **1a,b** shown in Schemes II and III represent the averages of measurements on the ^{13}C resonances of five different carbon atoms of ketals **6a,b**.

The ee's of the optically active cis and trans alcohols produced in the enzyme-mediated reductions, and recovered from the HLADH-catalyzed oxidations, were established by preparing their MTPA esters **7a,b** and **8a,b**, respectively. The behaviors of the methoxyl peaks were monitored in the presence of Eu(fod)$_3$.[14] The $\Delta\Delta\delta$ values for the MTPA esters of the racemic alcohols used as reference standards are recorded in Table III.

Absolute Configuration Determinations. The absolute configurations of the optically active thiopyranones depicted in Schemes II and III were assigned by octant rule[15] analyses of the Cotton effects manifest in their CD spectra. Two negative peaks, at ~290 and ~240 nm, were observed in the spectra of ethanolic solutions of each of (−)-**1a** and (−)-**1b**. These are attributed to the expected n–π^* transition (290 nm) and to a transannular charge-transfer interaction (240 nm)[16] between the sulfide and carbonyl groups. With the thiopyran rings of (−)-**1a,b** in their preferred chair conformations,[17] with equatorially oriented alkyl substituents, the CD results are unequivocally interpretable by using the well-documented 2-alkylcyclohexanone analyses.[18] The negative Cotton effects correspond to the (−) enantiomers of **1a,b** having 3*S* configurations. The sulfur atoms do not affect the octant rule analyses[19] in this case since they are in the nodal plane of the carbonyl group and therefore do not contribute to the rotatory strength.[15] The 3*R* configurations of **1a,b** of Scheme III then followed from their (+) rotations.

For the optically active cis and trans alcohols of Schemes II and III, the relative configurations of their chiral centers were established by NMR spectral comparisons with the fully characterized racemates (±)-**2a,b** and **3a,b**. The absolute configurations at C-3 of the cis alcohols (+)-**2a,b** and their trans isomers (+)-**3a,b** were determined by oxidation under neutral conditions to the corresponding (−)-(3*R*)- or (+)-(3*S*)-thiopyranones **1a,b**.

Discussion

While 3-substituted tetrahydrothiopyran-4-ones can be obtained via Dieckmann cyclizations of appropriately substituted derivatives of diester **4**,[20] such reactions are low yielding. Furthermore, every substituted thiopyranone must be prepared individually, since different intermediates are required in each case. Accordingly, the more flexible route shown in Scheme I was developed. This is generally applicable to 3-substituted ketones such as **1a,b**, with the desired alkyl groups being readily introduced into the common intermediate **5**. Good yields of (±)-**1a,b** were obtained by using this method.

In lithium aluminum hydride reductions of cyclohexanone, axial delivery of hydride is much preferred.[21] However, in **1a,b** the steric effects of the alkyl groups adjacent to the carbonyl group override this factor and, as in the reduction of 2-methylcyclohexanone,[22] formation of the trans alcohols becomes slightly favored. Reduction of (±)-**1a** and (±)-**1b** afforded the corresponding cis and trans alcohol products in 37:63 and 49:51 ratios, respectively. The identities of the individual stereoisomers were verified by examination of the C-4 ^1H NMR peaks.[8] The broad (22–24-Hz half-width) peaks of the axial C-4 protons of the trans alcohols **3a,b** resonated at 0.62–0.67 ppm higher field than the narrower (10-Hz half-width) bands of the corresponding equatorial protons of their cis isomers **2a,b**. Also, the shielding effect[8] of the 3-alkyl groups of **2a,b** and **3a,b** was found to cause a 0.18–0.38-ppm upfield shift of the C-4 proton resonances relative to those of their 2-alkylthiopyran-4-ol isomers.[4a]

Each preparative HLADH-catalyzed reaction was performed by using very simple procedures on a synthetically significant scale [~2 g of (±)-**1a,b** and ~0.3 g of (±)-**3a,b**]. The oxidoreductions were monitored by GLC, and, in accordance with our normal practice for racemates,[4] each reaction was terminated after ~50% of the substrate has been transformed. A workup via continuous chloroform extraction and chromatography resulted in virtually quantitative recovery of materials and afforded isolated, purified products in overall yields of 70–80%.

The direct ^{13}C and ^1H NMR-based ee determination methods previously found to be satisfactory in the 2-substituted thiopyran series[4a] proved flexible and accurate for measuring the ee levels of the optically active 3-alkylthiopyran ketones and alcohols of Schemes II and III. The absolute configurations shown in Schemes II and III were also established without difficulty. Octant rule analyses of the CD spectra of the ketones (−)-(3*S*)-**1a,b** were unambiguous. The assignments of the configurations of the chiral centers of (+)-**2a,b** and (+)- and (−)-**3a,b**, first by their identification as cis or trans isomers and then by their individual oxidations to the corresponding chiral ketones (+)-(3*S*)- or (−)-(3*R*)-**1a,b**, were similarly straightforward.

HLADH is seen to be very stereoselective in its oxidoreductions of 3-alkylthiopyran substrates, with the enantiomeric purities of the alcohols produced during reduction (Scheme II) and recovered following oxidation (Scheme III) being very high. The ee's of the ketones (−)-(3*S*)-**1a,b** recovered from the reduction procedures (Scheme II) are somewhat lower due to partial nonenzymic epimerization at C-3 during the pH 7, but somewhat

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lengthy, reaction period. The optical purities of the corresponding ketones formed during oxidation of the trans alcohols (±)-**3a,b** (Scheme III) are lower still, owing to the greater degree of epimerization occurring under the slightly basic (pH 9) conditions used for the oxidation reactions.

In the reduction mode, the virtually exclusive enantioselectivity of HLADH for the (3*R*) enantiomers of the thiopyranones **1a,b**, with hydride delivery to the *Re* face of the carbonyl group to give the trans alcohols (3*R*,4*S*)-**3a,b**, is as expected by analogy with HLADH-catalyzed 2-alkylcyclohexanone reductions.[2a,7,23] The amounts of the cis alcohols (3*R*,4*S*)-**2a,b** formed are very minor and are clearly of no preparative significance.[24] The Scheme II data are also in accord with the predictions of the cubic-space section model of the active site of the enzymes, with the cubic model analysis of the stereochemistry of HLADH-catalyzed reductions of (±)-**1a,b** being equivalent to those already detailed for their carbocyclic analogues.[25] The stereochemical course of oxidation of the trans alcohols (±)-**3a,b**, and the sluggish substrate behavior of the cis isomers (±)-**2a,b**, are similarly in accord with the cubic model predictions.[25]

Experimental Section

Unless otherwise indicated the instrumentation and general purification and analytical procedures used were as described previously.[1,2b] NAD^+ was purchased from Kyowa Hakko Kogyo, New York. HLADH (EC 1.1.1.1), prepared by the method of Roy and Nishikawa,[26] was a gift from Hoffmann-La Roche Inc. Equivalent material can be purchased from Sigma. The activity of each batch of enzyme was determined[27] prior to use, and the amounts of HLADH quoted refer to milligrams of active enzyme. Unless otherwise indicated, IR spectra were determined on liquid films and ^1H NMR spectra and optical rotations in C^2HCl_3 and $CHCl_3$ solutions, respectively.

Preparation of the Potassium Salt of 3-Carbomethoxytetrahydrothiopyran-4-one (5). Methyl acrylate and hydrogen sulfide were reacted by the method of Gershbein and Hurd[28] to give dimethyl 3,3-dithiopropanoate: 89% yield; bp 151–153 °C (5.5 mmHg) [lit.[28] bp 161–162 °C (18 mmHg)]. This diester was then converted in 71% yield as described by Fehnel and Carmack[29] to 3-carbomethoxytetrahydrothiopyran-4-one, bp 112–120 °C (1.3 mmHg) [lit.[29] bp 120–125 °C (5 mmHg)].

3-Carbomethoxytetrahydrothiopyran-4-one (40.3 g, 0.231 mol) was added during 3 min with stirring to a cooled (5–10 °C) solution of potassium hydroxide (13.0 g, 0.231 mol; 15.2 g of 85.6% purity) in water (6 mL) and methanol (63.5 mL), with care being taken to keep the temperature below 20 °C.[30] After 2 min ether (12 mL) was added. The pasty precipitate formed was filtered under suction immediately and washed with ice-cold methanol (15 mL) and then with ether (15 mL). The white solid obtained was pressed damp-dry on filter paper and then dried in vacuo for 8 h to give the potassium enolate **5** (41.7 g, 85% yield). This was used directly without further purification as described below.

Preparation of Thiopyran-4-ones (±)-1a,b. Both were prepared from the common intermediate **5**.

3-Methyltetrahydrothiopyran-4-one ((±)-1a).[20,29,31] Methyl iodide (26.7 g, 0.188 mol) was added dropwise with stirring at 20 °C under N_2 during 1 h to the above potassium enolate of 3-carbomethoxytetrahydrothiopyran-4-one (**5**; 20.2 g, 0.0942 mol) in dry dimethyl sulfoxide (175 mL). The mixture was stirred for a further 14 h at 20 °C, poured into water, and extracted with chloroform (3×). The chloroform extract was washed with water (3×), with aqueous sodium thiosulfate (2×), and again with water (2×) and then dried ($MgSO_4$). Evaporation of the chloroform solution yielded 3-carbomethoxy-3-methyltetrahydrothiopyran-4-one: 12.7 g (72% yield); bp 100–120 °C (0.16 mmHg); IR 1708, 1725, 1740 cm^{-1}; ^1H NMR (CCl_4) δ 1.33 (3 H, s), 2.5–3.3 (4 H, m), 2.90 (2 H, q, J = 14 Hz), 3.73 (3 H, s).

The above material (12.7 g, 0.0675 mol) in 10% aqueous sulfuric acid (150 mL) was refluxed with stirring for 19 h (bath temperature 120 °C). The mixture was then cooled and extracted with dichloromethane (3×). The dichloromethane extract was washed successively with water (2×), with saturated aqueous sodium bicarbonate, and finally with water (2×). The dried ($MgSO_4$) dichloromethane solution was evaporated to give a yellow oil (8.8 g) which on Kugelrohr distillation yielded 3-methyltetrahydrothiopyran-4-one ((±)-**1a**): 5.64 g (64% yield); bp 68–69 °C (3 mmHg) [lit.[20] bp 43–48 °C (1.5 mmHg)]; IR (CCl_4) 1710 cm^{-1}; ^1H NMR δ 1.10–1.20 (3 H, complex d, J = 6 Hz), 2.55–3.2 (7 H, m); MS, m/e (relative intensity) 130 (6), 102 (7), 88 (24), 74 (100).

3-Ethyltetrahydrothiopyran-4-one ((±)-1b). The potassium enolate **5** (21.5 g, 0.101 mol) was treated with ethyl iodide (28.9 g, 0.185 mol) as described above to give 3-carbomethoxy-3-ethyltetrahydrothiopyran-4-one: 18.9 g (92% yield); bp 100 °C (0.1 mmHg); IR 1703, 1720, 1735 cm^{-1}; ^1H NMR δ 0.88 (3 H, t, J = 7 Hz), 1.84 (2 H, q, J = 7 Hz), 2.1–3.5 (6 H, m), 3.8 (3 H, s); MS, m/e (relative intensity) 202 (12), 173 (100), 141 (55), 115 (43), 88 (33). This keto ester (2.45 g, 0.012 mol) in 10% sulfuric acid (150 mL) was refluxed with stirring for 29 h (bath temperature 160 °C) and worked up as for (±)-**1a** to give a pale orange oil (1.54 g) which on Kugelrohr distillation afforded 3-ethyltetrahydrothiopyran-4-one: 1.37 g (78% yield); bp 75 °C (0.25 mmHg); IR (CCl_4) 1709 cm^{-1}; ^1H NMR δ 0.93 (3 H, t, J = 7 Hz), 1.1–3.3 (9 H, m). Anal. Calcd for $C_7H_{12}OS$: C, 58.29; H, 8.39; S, 22.23. Found: C, 58.13; H, 8.36; S, 22.12.

Preparations of Cis and Trans Alcohols (±)-2a,b and (±)-3a,b. The ketones (±)-**1a,b** were reduced with lithium aluminum hydride as described previously.[4a] The cis and trans alcohol mixtures obtained were separated by MPLC on silica (ICN, 0.032–0.063 mm) with ethyl acetate–hexane (1:5) elution. The products obtained were as follows.

***cis*- and *trans*-3-Methyltetrahydrothiopyran-4-ol (±)-2a and (±)-3a.** The cis–trans (37:43) mixture (1.36 g, 10 mmol) from reduction of (±)-**1a** (1.3 g, 10 mmol) gave the **cis alcohol (±)-2a**: 436 mg (33% yield); bp 75 °C (0.15 mmHg); IR 3400 cm^{-1}; ^1H NMR δ 1.05 (3 H, d, J = 7 Hz), 1.2–3.2 (8 H, m), 3.82 (1 H, m, $W_{1/2}$ = 10 Hz). Anal. Calcd for $C_6H_{12}OS$: C, 54.50; H, 9.15; S, 24.25. Found: C, 54.39; H, 9.03; S, 24.15.

Trans alcohol (±)-3a: (55% yield); bp 83 °C (0.20 mmHg); mp 32–33.5 °C; IR 3370 cm^{-1}; ^1H NMR δ 1.10 (3 H, d, J = 6.5 Hz), 1.30–2.85 (8 H, m), 3.15 (1 H, m, $W_{1/2}$ = 24 Hz). Anal. Calcd for $C_6H_{12}OS$: C, 54.50; H, 9.15; S, 24.25. Found: C, 54.59; H, 9.10; S, 24.41.

***cis*- and *trans*-3-Ethyltetrahydrothiopyran-4-ol (±)-2b and (±)-3b.** The cis–trans (49:51) mixture (1.46 g, 10 mmol) from reduction of (±)-**1b** (1.44 g, 10 mmol) yielded the **cis alcohol (±)-2b**: 590 mg (40% yield); bp 110 °C (0.3 mmHg); IR 3400 cm^{-1}; ^1H NMR δ 0.93 (3 H, t, J = 6 Hz), 1.15–3.22 (10 H, m); 3.92 (1 H, m, $W_{1/2}$ = 10 Hz). Anal. Calcd for $C_7H_{14}OS$: C, 57.49; H, 9.65; S, 21.92. Found: C, 57.50; H, 9.78; S, 22.08.

Trans alcohol (±)-3b: 630 mg (43% yield); bp 100 °C (0.15 mmHg); mp 25.5–27 °C; IR 3380 cm^{-1}; ^1H NMR δ 0.90 (3 H, t, J = 6 Hz), 1.0–3.00 (10 H, m), 3.30 (1 H, m, $W_{1/2}$ = 22 Hz). Anal. Calcd for $C_7H_{14}OS$: C, 57.49; H, 9.65; S, 21.92. Found: C, 57.43; H, 9.78; S, 21.84.

Relative Rates of HLADH-Catalyzed Reductions of (±)-1a,b and Oxidations of (±)-2a,b and (±)-3a,b. Assays were performed as described previously[2b,4a] on solutions 10^{-3} M in (±)-**1a,b** and 6×10^{-3} M in (±)-**2a,b** and (±)-**3a,b**. The results are summarized in Table I.

HLADH-Catalyzed Reductions of (±)-1a,b. The same general procedure[4] was used for both substrates. The 3-alkyl-

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(24) However, the fact that cis alcohols are formed at all is of considerable stereochemical interest with respect to the enzyme since such cis products have not been reported in previous studies on HLADH-catalyzed 2-alkylcyclohexanone reductions.[2a,8,22] Accordingly, this aspect has been studied in detail and will be reported shortly.

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thiopyranone (~2 g) was dissolved in 0.1 M potassium phosphate buffer (pH 7, 1 L) at room temperature (20 °C) in a 2-L Erlenmeyer flask. NAD^+ (~1.7 g) and ethanol (3 mL) were then added, and the pH was readjusted to 7 with 10 M aqueous potassium hydroxide. The reduction was initiated by the addition of HLADH (80–100 mg). After 4 days, more NAD^+ (1.5 g) was added, the pH readjusted to 7, and further HLADH (80 mg) added. The extent of reaction was monitored by GLC, and after ~50% of reduction (8–11 days) the mixture was continuously extracted with chloroform for 2 days. The dried ($MgSO_4$) chloroform extract was evaporated and the residue (quantitative recovery) purified by MPLC on silica [ethyl acetate–hexane (1:5) elution] to give the unreacted optically active ketones (−)-**1a,b** and product alcohols (+)-**2a,b** and (+)-**3a,b**. The spectral properties of each compound were identical with those of the corresponding racemates characterized previously.

The individual reactions gave the following results (cf. Scheme II) after Kugelrohr distillation of each chromatographically purified compound.

Reduction of (±)-1a (2.02 g, 15.5 mmol) with HLADH (169 mg), NAD^+ (3.19 g, 4.81 mmol), and EtOH (3 mL) for 8 days (49% reduction) gave the following. (−)-(3*S*)-**1a**: 0.38 g (66% ee) bp 85 °C (5 mmHg); $[\alpha]^{20}_D$ −22.4° (*c* 1). (+)-(3*S*,4*S*)-**2a**: 46 mg (60% ee); bp 83 °C (2 mmHg); $[\alpha]^{20}_D$ +2.1° (*c* 0.7). (+)-(3*R*,4*S*)-**3a**: 1.02 g (90% ee); bp 79 °C (1.5 mmHg); mp 41.5–42 °C; $[\alpha]^{20}_D$ +30.2° (*c* 1.1).

Reduction of (±)-1b (2.02 g, 14 mmol) with enzyme (181 mg), NAD^+ (3.21 g, 4.84 mmol), and EtOH (3 mLe for 11 days (51% reduction) yielded the following. (−)-(3*S*)-**1b**: 0.65 g (58% ee); bp 92 °C (7 mmHg); $[\alpha]^{20}_D$ −36.0° (*c* 1). (+)-(3*S*,4*S*)-**2b**: 56 mg (93% ee); bp 81 °C (2.5 mmHg); $[\alpha]^{20}_D$ +14.7° (*c* 0.53). (+)-(3*R*,4*S*)-**3b**: 0.97 g (78% ee); bp 90 °C (2.5 mmHg) mp 52–53 °C; $[\alpha]^{20}_D$ +39.5° (*c* 1.1).

HLADH-Catalyzed Oxidations of (±)-3a,b. The general experimental workup, and analytical procedures for HLADH-catalyzed oxidations[32] were employed. They parallel those described above for the reduction reactions. The results obtained (cf. Scheme III) are as follows.

Oxidation of (±)-3a. The *trans*-3-methyl alcohol (±)-**3a** (332 mg, 2.5 mmol), NAD^+ (432 mg, 0.64 mmol), FMN (4.78 g, 9.9 mmol), and HLADH (28 mg) in 0.05 M glycine–NaOH buffer (pH 9, 400 mL) in a 1-L Erlenmeyer flask was kept at 20 °C for 6 days (~50% oxidation by GLC). The workup yielded (+)-(3*R*)-**1a** [106 mg (20% ee); bp 68 °C (2 mmHg); $[\alpha]^{20}_D$ +6.1 °C (*c* 1.1)] and (−)-(3*S*,4*R*)-**3a**: 112 mg (85% ee); bp 80 °C (1.2 mmHg); $[\alpha]^{20}_D$ −32.0° (*c* 1.1).

Oxidation of (±)-3b. The *trans*-3-ethyl alcohol (325 mg, 2.2 mmol), NAD^+ (348 mg, 0.52 mmol), FMN (3.49 g, 7.2 mmol), and HLADH (22 mg) in 0.05 M glycine–NaOH buffer (pH 9, 600 mL) was kept at 20 °C for 6 days (~50% oxidation by GLC). The workup gave (+)-(3*R*)-**1b** [93 mg (15% ee); bp 80 °C (2.7 mmHg); $[\alpha]^{20}_D$ +15.0° (*c* 0.9)] and (−)-(3*S*,4*R*)-**3b**: 123 mg (65% ee); bp 80 °C (1.2 mmHg); $[\alpha]^{20}_D$ −32.8° (*c* 1.2).

Enantiomeric Excess Determinations of Ketones 1a and 1b. Each racemic and optically active ketone **1a,b** (1 mmol) was converted to its ketal **5a,b** by heating under reflux in benzene (20 mL) with (−)-(2*R*,3*R*)-2,3-butanediol (1.3 mmol) and *p*-toluenesulfonic acid (5 mg) in a Dean–Stark apparatus for 18 h. The benzene solution was then evaporated, and the residue was dissolved in ether (50 mL) and washed with 10% aqueous sodium hydroxide (3 × 20 mL) followed by water (4 × 50 mL) until neutral. The dried ($MgSO_4$) ether solution was then evaporated to give the ketals **5a,b** in quantitative yields. Each ketal was Kugelrohr distilled and its ^1H decoupled ^{13}C NMR spectrum determined. These are recorded below for the racemic ketals. The ee values of the ketals derived from optically active ketones of Schemes II and III were determined from their ^{13}C NMR spectra by the method of Hiemstra and Wynberg[12] using the enantiomeric shift differences indicated in Table II.

3-Methyltetrahydrothiopyran-4-one ketal 6a: bp 85 °C (5 mmHg); ^{13}C NMR δ 14.19 and 14.29 (CH_3), 16.16 and 16.25 (C-9), 17.65 (C-10), 26.84 and 26.95 (C-6), 33.51 (C-2), 37.52 and 37.97 (C-5), 41.00 and 41.75 (C-3), 77.73 and 78.01 (C-7), 79.38 and 79.83 (C-8), 108.25 (C-4).

3-Ethyltetrahydrothiopyran-4-one ketal 6b: bp 90 °C (5 mmHg); ^{13}C NMR δ 11.79 (CH_2CH_3), 16.34 (C-9), 17.58 and 17.67 (C-10), 20.08 and 20.21 (CH_2CH_3), 26.56 and 26.74 (C-6), 30.16 (C-2), 37.30 and 37.50 (C-5), 47.94 and 48.52 (C-3), 77.79 and 77.92 (C-7), 79.28 (C-8), 108.32 and 108.49 (C-4).

Enantiomeric Excess Determinations of Alcohols 2a,b and 3a,b. The racemic and optically active alcohols **2a,b** and **3a,b** (30 mg) were each converted to their MTPA esters **7a,b** and **8a,b** in quantitative yields by the literature procedure[14] using freshly prepared (+)-(2*R*)-methoxy[2-(trifluoromethyl)phenyl]acetyl (MTPA) chloride: 100 mg (~1.9 equiv); $[\alpha]^{25}_D$ 131.9° (*c* 1, CCl_4) [lit.[14] $[\alpha]^{24}_D$ +129.0 ± 0.2° (*c* 5.17, CCl_4)]. The enantiomeric purities of the MTPA esters of the Scheme II and III cis and trans alcohols were then determined by 60-MHz ^1H NMR examination of the methoxyl resonances in the presence of $Eu(fod)_3$. The spectra and properties of the Kugelrohr-distilled Mosher esters of the racemic alcohols (±)-**2,3a,b** used as references for establishing the ΔΔδ values of each pair of diastereotopic methoxyl groups[14] (summarized in Table III) are as follows.

***cis*-3-Methyltetrahydrothiopyran-4-ol (7a)**: bp 100 °C (0.3 mmHg); IR (CCl_4) 1747 cm^{-1}; ^1H NMR (CCl_4) δ 0.85 and 1.0 (3 H, dd, *J* = 7 Hz), 1.7–3.1 (7 H, m), 3.55 (3 H, br s), 5.15 (1 H, m, $W_{1/2}$ = 9 Hz), 7.2–7.7 (5 H, m).

MTPA Ester of *cis*-3-Ethyltetrahydrothiopyran-4-ol (7b): bp 100 °C (0.24 mmHg); IR (CCl_4) 1746 cm^{-1}; ^1H NMR (CCl_4) δ 0.97 (3 H, t, *J* = 6 Hz), 1.1–2.9 (9 H, m), 3.55 (3 H, br s), 5.3 (1 H, m, $W_{1/2}$ = 9 Hz), 7.2–7.7 (5 H, m).

MTPA Ester of *trans*-3-Methyltetrahydrothiopyran-4-ol (8a): bp 95 °C (0.2 mmHg); IR (CCl_4) 1750 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 and 1.10 (3 H, dd, *J* = 6.6, 6.2 Hz), 1.5–3.0 (7 H, m), 1.55 (3 H, m), 1.65 (1 H, m, $W_{1/2}$ = 21 Hz), 7.45 (5 H, m).

MTPA Ester of *trans*-3-Ethyltetrahydrothiopyran-4-ol (8b): bp 94 °C (0.15 mmHg); IR (CCl_4) 1745 cm^{-1}; ^1H NMR (CCl_4) δ 0.84 (3 H, br t, *J* = 7 Hz), 1.15–3.1 (9 H, m), 3.55 (3 H, m), 4.8 (1 H, m, $W_{1/2}$ = 22 Hz), 7.4 (5 H, m).

Absolute Configuration Determinations. (1) Of the Enzyme-Derived Ketones (+)- and (−)-1a,b. These were established by octant rule analyses of the Cotton effects observed in the CD spectra of (−)-**1a,b** recovered from the HLADH-catalyzed reduction experiments (Scheme II). The spectral data used were as follows: (−)-(3*S*)-**1a** (*c* 0.009, EtOH, 20 °C) $[\theta]_{320}$ 0°, $[\theta]_{285}$ −725°, $[\theta]_{268}$ (trough) −591°, $[\theta]_{238}$ −3790°, $[\theta]_{210}$ 0°; (−)-(3*S*)-**1b** (*c* 0.009, EtOH, 20 °C) $[J]_{330}$ 0°, $[\theta]_{293}$ −1620°, $[\theta]_{265}$ (trough) −809°, $[\theta]_{240}$ −3680°, $[\theta]_{210}$ 0°. The absolute configurations of (+)-**1a,b** isolated from the Scheme III reactions were then assigned on the basis of their signs of optical rotations.

(2) Of the Optically Active Alcohols (+)-2a,b and (+)- and (−)-3a,b. The relative configurations at C-3 and C-4 of the cis and trans alcohols were established by reference to the ^1H NMR spectra of the fully characterized racemates (±)-**2a,b** and (±)-**3a,b** detailed above.

The absolute configurations at the C-3 centers of (+)-**2a,b** and (+)-**3a,b** were then determined by oxidation of each to the corresponding ketones (+)- or (−)-**1a,b** of the known absolute configurations determined above. The oxidations were carried out under neutral conditions in order to minimize (while not wholly preventing) the extent of epimerization of the product ketones during the reactions.

Oxidation of (+)-2a,b and (+)-3a,b. The cis alcohols (+)-**2a,b** were oxidized on a 0.2-mmol scale with *N,N*-dicyclohexylcarbodiimide–dimethyl sulfoxide by using the method of Paquette and Wise.[33] Oxidation of the trans stereoisomer (+)-**3a,b** (0.5 mmol) was effected with pyridinium chlorochromate (0.77 mmol) in dichloromethane containing sodium acetate according to the procedure of Corey and Suggs.[34] The ketone products were purified as described for the enzyme-mediated oxidoreductions, and their properties and spectral data were identical with those of the previous samples: (+)-**2a** gave (−)-(3*S*)-**1a** (20% yield) $[\alpha]^{20}_D$ −9.5° (*c* 0.1); (+)-**2b** yielded (−)-(3*S*)-**1b** (55% yield) $[\alpha]^{20}_D$ −40.4° (*c* 0.3); (+)-**3a** afforded (+)-(3*R*)-**1a** (29% yield) $[\alpha]^{20}_D$ +17.3° (*c*

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0.12); (+)-**3b** gave rise to (+)-(3*R*)-**1b** (27% yield) $[\alpha]^{20}_D$ +23.8° (*c* 0.13).

The C-3 and C-4 chiralities of (−)-**3a,b** followed from their enantiomeric relationships to those of the corresponding (+) stereoisomers. The overall absolute configuration assignments are summarized in Schemes II and III.

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Registry No. (±)-**1a**, 84583-08-4; (−)-(3*S*)-**1a**, 84622-33-3; (+)-(3*R*)-**1a**, 84622-39-9; (±)-**1b**, 84583-10-8; (−)-(3*S*)-**1b**, 84622-36-6; (+)-(3*R*)-**1b**, 84622-41-3; (±)-**2a**, 84583-11-9; (+)-(3*S*,4*S*)-**2a**, 84622-34-4; (±)-**2b**, 84583-13-1; (+)-(3*S*,4*S*)-**2b**, 84622-37-7; (±)-**3a**, 84583-12-0; (+)-(3*R*,4*S*)-**3a**, 84622-35-5; (−)-(3*S*,4*R*)-**3a**, 84622-40-2; (±)-**3b**, 84583-14-2; (+)-(3*R*,4*S*)-**3b**, 84622-38-8; (−)-(3*S*,4*R*)-**3b**, 84622-42-4; **5**, 84583-06-2; 3-carbomethoxy-3-methyltetrahydrothiopyran-4-one, 84583-07-3; 3-carbomethoxy-3-ethyltetrahydrothiopyran-4-one, 84583-09-5; alcohol dehydrogenase, 9031-72-5.

Electronic Structure and Reactivity of Homobarrelene Derivatives

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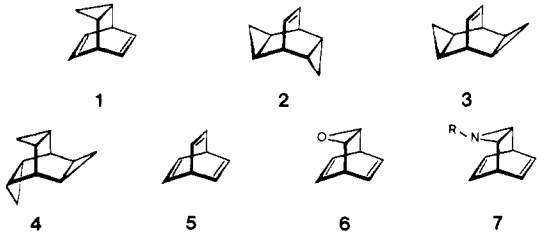
The He(I) photoelectron (PE) spectra of homobarrelene (**1**), *endo,exo*- and *exo,exo*-dihomobarrelene (**2** and **3**) and trihomobarrelene (**4**) have been investigated. The first bands in the PE spectra of **1**–**4** are assigned on the basis of MINDO/3 and INDO calculations. The localized orbitals derived from INDO calculations are used to discuss the through-bond and through-space interaction present in **1**–**4**. The results of this analysis are used to rationalize the stereochemistry observed for the reaction of **1** and the hetero derivatives **6** and **7** with carbene, nitrene, and peracids.

In recent years the interaction between the valence orbitals of a cyclopropane moiety and π bonds has been studied extensively by means of low-energy photoelectron (PE) spectroscopy.[1-8] It has been demonstrated that the interaction between the π system and the three-membered-ring fragment critically depends on the orientation between both units and that a through-space and a through-bond[9] coupling mechanism can be used to describe the interactions.

In this paper we analyze the He(I) photoelectron (PE) spectra of various barrelene derivatives containing a three-membered ring instead of a double bond. The hydrocarbons are homobarrelene (**1**), *endo,exo*- and *exo,exo*-dihomobarrelene (**2** and **3**), and trihomobarrelene (**4**). The PE spectra of **1**–**4** are compared with the spectrum of barrelene (**5**).[10]



A second aim of this paper is to evaluate the magnitude of through-space and through-bond interactions in these species and to rationalize the strikingly different regiochemistry of the cheletropic cycloadditions of methylene, nitrene, and "oxene" (from *m*-chloroperbenzoic acid) to **1**, **6**, and **7**.

Photoelectron Spectra

The PE spectra of **1**–**4** are shown in Figure 1, and the vertical ionization potentials are collected in Table I. To assign the first bands in the PE spectra of **1**–**4**, we assume the validity of Koopmans' theorem[11] shown in eq 1. This

$$I_{V,J}{}^{K} = -\epsilon_J \qquad (1)$$

assumption allows us to compare the measured vertical ionization potentials, $I_{V,J}$, with calculated orbital energies, ϵ_J, using molecular orbital (MO) models. To derive the orbital energies, we use a recently developed INDO approximation[12] and the MINDO/3[13] method. The geometries of **1**–**5** correspond to the energy minimum obtained by the MINDO/3 method by optimizing the total energy with respect to the geometrical variables.

The PE spectrum of **5**[10] shows two bands below 10 eV which have been assigned to ionization events from the π

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