(*E*)-3-(Methoxycarbonyl)-2-propenyl Tetrahydropyranyl Ether (3b). A solution of **3a**[11] (2.32 g, 20 mmol) and dihydropyran (1.82 mL, 20 mmol) containing 1 drop of concentrated HCl was stirred for 2 h at room temperature. Ether was added, and the organic phase was washed with saturated $NaHCO_3$ and water and dried (Na_2SO_4). Evaporation of the solvent and bulb-to-bulb distillation of the residue (0.1 mmHg, 80–85 °C, oven temperature) furnished 3.35 g (84%) of **3b**: UV λ_{max} 207 nm (ϵ 10900); ^{1}H NMR δ 1.3–2.0 (6 H, m, THP), 3.3–4.0 (2 H, m, THP), 3.73 (3 H, s, CO_2Me), 4.13 and 4.43 (2 H, ddd, J = 16.5, 4.5, and 1.5 Hz, C-1 H_2), 4.67 (1 H, m, THP), 6.13 (1 H, dt, J = 16.5 and 1.5 Hz, C-3 H), 7.03 (1 H, dt, J = 16.5 and 4.5 Hz, C-2 H).

Anal. Calcd for $C_{10}H_{16}O_4$ (200.2): C, 59.98; H, 8.05. Found: C, 60.00; H, 8.15.

Methyl (*Z*)-3β-Acetoxy-21-[(tetrahydropyranyl)oxy]-24-nor-5α-chola-16,20(22)-dien-23-oate (4c). A mixture of **2a** (0.46 g, 1 mmol), **3b** (0.30 g, 1.5 mmol), tributylamine (0.48 mL, 2 mmol), palladium acetate (11 mg, 0.05 mmol), and triphenylphosphine (26 mg, 0.10 mmol) in DMF (4 mL) was stirred at 80 °C for 24 h, under nitrogen. The reaction was then diluted with water, extracted with ether, washed with 2 N HCl and then water until neutral, dried (Na_2SO_4), and evaporated. Chromatography of the residue (0.63 g) on deactivated (grade II) Woelm neutral alumina (32 g) using benzene as eluent and further purification of the main fractions (0.27 g) on silica gel (14 g) with benzene–ethyl acetate (97:3) as eluent gave 204 mg (40%) of **4c**: mp 105–106 °C (from hexane); $[\alpha]_D$ −6°; UV λ_{max} 279 nm (ϵ 12900); IR 1727 (C=O), 1613 (C=C) cm^{-1}; ^{1}H NMR δ 0.83 (3 H, s, 10-Me), 0.93 (3 H, s, 13-Me), 1.98 (3 H, s, 3β-OAc), 3.4–4.1 (2 H, m, THP), 3.69 (3 H, s, CO_2Me), 4.5–5.0 (4 H, m, THP, C-21 H_2, and 3α-H), 6.00 (1 H, s, C-22 H), 6.28 (1 H, m, C-16 H).

Anal. Calcd for $C_{31}H_{46}O_6$ (514.7): C, 72.34; H, 9.01. Found: C, 72.28; H, 9.13.

3β-Hydroxy-5α,14α-carda-16,20(22)-dienolide Acetate (5a). A mixture of **4c** (103 mg, 0.2 mmol) and Dowex-50W × 8 resin (200–400 mesh, H^+ form, 100 mg) in CH_2Cl_2 (1 mL) and MeOH (4 mL) was stirred at 45–50 °C for 2 h. Filtration of the resin and evaporation of the solvent furnished 72 mg (90%) of almost pure **5a**: mp 235.5–237 °C (from methanol); $[\alpha]_D$ +29° (lit.[9a] mp 235–238 °C; $[\alpha]_D$ +37°); UV λ_{max} 272 nm (ϵ 16800); IR 1783, 1744 (lactone C=O), 1730 (acetate C=O), 1614 (C=C) cm^{-1}; ^{1}H NMR δ 0.85 (3 H, s, 10-Me), 0.92 (3 H, s, 13-Me), 2.00 (3 H, s, 3β-OAc), 4.7 (1 H, m, 3α-H), 4.95 (2 H, br s, C-21 H_2), 5.97 (1 H, br s, C-22 H), 6.18 (1 H, m, C-16 H).

The procedure was repeated on the residue (0.56 g) of the palladium-catalyzed coupling, directly. The new residue (0.47 g) was chromatographed on silica gel (23 g); elution with benzene–ethyl acetate (97:3) afforded 158 mg (40%) of **5a**.

Repetition of the coupling–cyclization sequence on **2b** in the same conditions as used for **2a** gave 147 mg (37%) of **3β-hydroxy-5β,14α-carda-16,20(22)-dienolide acetate (5b)**: mp 227–229 °C (from acetone–hexane); $[\alpha]_D$ +46°; UV λ_{max} 272 nm (ϵ 17800); IR 1785 (lactone C=O), 1741 (lactone and acetate C=O), 1610 (C=C) cm^{-1}; ^{1}H NMR δ 0.92 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 2.02 (3 H, s, 3β-OAc), 4.93 (2 H, br s, C-21 H_2), 5.10 (1 H, m, 3α-H), 5.97 (1 H, br s, C-22 H), 6.17 (1 H, m, C-16 H).

Anal. Calcd for $C_{25}H_{34}O_4$ (398.5): C, 75.34; H, 8.60. Found: C, 75.21; H, 8.50.

3β-Hydroxy-5α,14α-card-20(22)-enolide Acetate (6a). **5a** (100 mg) in ethyl acetate (20 mL) was hydrogenated over 5% palladium on charcoal (20 mg) at room temperature and atmospheric pressure for 3 h. Filtration and evaporation gave 100 mg (99%) of **6a**: mp 191–192.5 °C (from methanol); $[\alpha]_D$ −1° (lit.[9b] mp 193–194 °C; $[\alpha]_D$ −1°); UV λ_{max} 219 nm (ϵ 12600); IR 1785, 1741 (lactone C=O), 1739 (acetate C=O), 1622 (C=C) cm^{-1}; ^{1}H NMR δ 0.60 (3 H, s, 13-Me), 0.82 (3 H, s, 10-Me), 2.00 (3 H, s, 3β-OAc), 4.7 (1 H, m, 3α-H), 4.65 and 4.87 (2 H, AB q, J = 18 Hz, C-21 H_2), 5.85 (br s, 1 H, C-22 H).

Hydrogenation of **5b** in the same conditions gave **3β-hydroxy-5β,14α-card-20(22)-enolide acetate (6b)**: mp 194–195 °C (from acetone–hexane); $[\alpha]_D$ +15° (lit.[9c] mp 195–197 °C; $[\alpha]_D$ +12°); UV λ_{max} 219 nm (ϵ 13800); IR 1791, 1754 (lactone C=O), 1727 (acetate C=O), 1631 (C=C) cm^{-1}; ^{1}H NMR δ 0.60 (3 H, s, 13-Me), 0.95 (3 H, s, 10-Me), 2.02 (3 H, s, 3β-OAc), 4.63 and 4.85 (2 H, AB q, J = 18 Hz, C-21 H_2), 5.10 (1 H, m, 3α-H), 5.83 (1 H, br s, C-22 H).

Methyl (*E*)-3β-Acetoxy-24-nor-5α-chola-16,20(22)-dien-23-oate (4b). A mixture of **2a** (0.46 g, 1 mmol), methyl crotonate (0.21 mL, 2 mmol), tributylamine (0.48 mL, 2 mmol), palladium acetate (11 mg, 0.05 mmol), and triphenylphosphine (26 mg, 0.10 mmol) in DMF (4 mL) was stirred at 80 °C for 9 h. Residue from usual workup (0.42 g) was chromatographed on silica gel (32 g) with benzene–ethyl acetate (99:1) as eluent to afford 228 mg (55%) of **4b**: mp 136–137 °C (from methanol); $[\alpha]_D$ −4°; UV λ_{max} 275 nm (ϵ 15100); IR 1739 (C=O), 1612 (C=C) cm^{-1}; ^{1}H NMR δ 0.83 (3 H, s, 10-Me), 0.92 (3 H, s, 13-Me), 1.98 (3 H, s, 3β-OAc), 2.28 (3 H, s, 20-Me), 3.68 (3 H, s, CO_2Me), 4.7 (1 H, m, 3α-H), 5.93 (1 H, br s, C-22 H), 6.13 (1 H, m, C-16 H).

Anal. Calcd for $C_{26}H_{38}O_4$ (414.6): C, 75.32; H, 9.24. Found: C, 75.39; H, 9.30.

Registry No. **1a**, 1239-31-2; **1b**, 4820-41-1; **1c**, 3959-78-2; **1d**, 7557-85-9; **2a**, 91934-55-3; **2b**, 96150-02-6; **2c**, 96095-92-0; **2c** (R = H, R_1 = α-H), 96095-93-1; **2d**, 96095-94-2; **3a**, 29576-13-4; **3b**, 96095-95-3; **4b**, 96095-96-4; **4c**, 96095-97-5; **5a**, 96095-98-6; **5b**, 96150-03-7; **6a**, 3697-94-7; **6b**, 6564-57-4; triflic anhydride, 358-23-6; methyl (*E*)-crotonate, 623-43-8.

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Enantioselective Oxidation of 1,2-Diols to L-α-Hydroxy Acids Using Coimmobilized Alcohol and Aldehyde Dehydrogenases as Catalysts[1]

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We have described before the biochemical aspects of enzyme catalysis with respect to the stereospecificity of the oxidation of 1,2-diols and α-amino alcohols catalyzed by alcohol dehydrogenases and the rationalization of the stereospecificity based on a cubic-space active-site section model.[3] Although both yeast and horse liver alcohol dehydrogenases were found to have the same enantioselectivity in the oxidations, the yeast enzyme was unstable and less active than the horse liver enzyme. In connection with our interest in developing practical enzymatic procedures for use in synthetic organic chemistry, we here report the preparation of several enantiomerically pure L-α-hydroxy acids from racemic 1,2-diols based on the stereospecificity of the oxidations observed,[3] in a process using coimmobilized alcohol dehydrogenase/aldehyde dehydrogenase as catalysts (Scheme I). As indicated in the scheme, the enzyme horse liver alcohol dehydrogenase (HLADH) catalyzes the enantioselective oxidation of a number of racemic 1,2-diols to L-α-hydroxy aldehydes which are further converted to L-α-hydroxy acids catalyzed by aldehyde dehydrogenase (AldDH). Both enzymatic reactions require NAD as a cofactor; a cofactor regeneration system is therefore incorporated into the synthetic scheme.

The α-hydroxy acids **3a–h** prepared here are useful in synthetic organic chemistry. L-α-Halolactic acid, for example, can be converted to L-glycidic acid for use as a synthon.[4] 3-Amino-2-hydroxypropionic acid has the

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(2) NSF Predoctoral Fellow.

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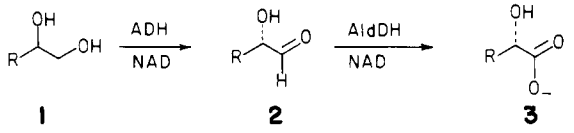
0022-3263/85/1950-1992$01.50/0

Scheme I



1 2 3

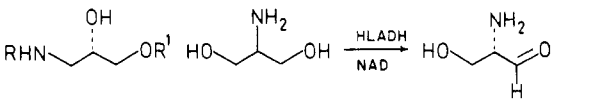
R: HOH_2C- **1a**—**3a**, FH_2C- **1b**—**3b**, ClH_2C- **1c**—**3c**, BrH_2C- **1d**—**3d**, H_3C- **1e**—**3e**, H_2NH_2C- **1f**—**3f**, $H_2C{=}CH$- **1g**—**3g**, H_3CH_2C- **1h**—**3h**, $(H_3C)_2$- **1i**—**3i**

correct configuration for the preparation of a number of β-adrenoceptor blocking agents,[5] **4**, which are currently prepared from D-mannitol or ascorbic acid via complicated procedures.

The synthetic reactions illustrated here rely upon the selective oxidation of one enantiomer in the presence of the other (except for meso diols glycerol, **1a**, and serinol, **1f**) and thus, in principle, yield a maximum of 50% of desired product on the basis of the racemic starting material. Although the D-diols are very poor substrates for HLADH,[3] the reactions were controlled so that only 40% of the racemic mixture would be transformed and enantiomerically pure product could be obtained. Even given this disadvantage, this is a more practical route to L-α-hydroxy acids than any other enzymatic system. The synthetic methodology described here provides an alternate approach to enantiomerically pure L-α-hydroxy aldehydes and L-α-hydroxy acids from readily available 1,2-diols. It overcomes the difficulty encountered in the preparation of α-hydroxy acids from α-keto acids using L-lactic dehydrogenase (L-LDH) as catalyst.[4] α-Keto acids are much more expensive and less stable than racemic diols and many of them are not commercially available. Also, β-halo α-keto acids would tend to inactivate enzymes via alkylation.[4] Although many chemical agents for use in the oxidation of alcohols are available, problems of overoxidation, racemization, and low regio- and enantioselectivity, particularly in the case of 1,2-diol systems,[6-8] usually result.

We note that the enzyme HLADH also accepts α-amino alcohols as substrates,[9] and the enantioselectivity in the oxidation of amino alcohols is the same as that in the oxidation of diols.[3] This enzymatic process provides an alternate route to α-amino aldehydes which currently are difficult to prepare.[10] Amino aldehydes in neutral aqueous solution are hydrated and more stable than in organic solvents. They can be isolated by trapping[9] or being converted in situ to other compounds. One interesting example is the oxidation of **5**, a prochiral amino alcohol, to L-α-amino-β-hydroxpropanal (**6**) enantioselectively with 96% ee.

One problem encountered in these reactions is that a dramatic decrease in enantioselectivity was observed when 1,2-diols and α-amino alcohols with hydrophobic β-substituents such as **1i** were used as substrates.[3]



4 5 6 96% ee

Experimental Section

Enzymes HLADH (EC 1.1.1.1), AldDH (EC 1.2.1.5), glutamic dehydrogenase (GluDH, EC 1.4.1.3), L-LDH (EC 1.1.1.27), and D-LDH (EC 1.1.1.28) were all purchased from Sigma and used without further purification. Compounds **1b** and **1g** were obtained via acid-catalyzed ring opening of the respective epoxides from Aldrich. Compounds **1c**, **1d**, **e**, **1f**, and (*S*)-**1e** were reagent grade and purchased from Aldrich. Compound **1a** was from MCB. Compound (*R*)-**1e** was prepared from L-threonine by treatment with ninhydrin and subsequent $NABH_4$ reduction of the lactaldehyde obtained.[11] A Beckman DU-6 spectrophotometer was used in monitoring enzymatic reactions. Enzymes were assayed according to the standard procedures.[12]

Determination of Optical Purity. D-Serine was determined with D-amino acid oxidase[12] and L-serine with alanine dehydrogenase[12] (L-serine is not a substrate for L-amino acid oxidase). The optical purity of D- and L-α-hydroxy acids was determined enzymatically with D- and L-LDH[3,12] with some modifications. To 2.8 mL of glycine/hydrazine buffer (0.5 M/0.4M, pH 9.0) was added 100 μL of D- or L-LDH solution (12 mg/mL) and 30 μL of NAD solution (1.0 M). The solution in the cuvette was allowed to stand for 30 min after which 100 μL of substrate solution (20 mM)[13] was added, and the mixture was monitored at 340 nm until no further change in absorbance was observed. The change of absorbance observed should reflect to the concentration of one enantiomeric α-hydroxy acid in the sample depending on which LDH is used. This enzymatic method for determination of the optical purity of the α-hydroxy acids is as accurate as that based on NMR measurement of the (*R*)-(+)-MTPA esters.[3] Both methods allow detection of 1.5% of one enantiomer in the presence of 98.5% of the other, indicating that enantiomeric escess as high as 97% can be determined. Compounds **3a–h** prepared here are all L enantiomers; the D enantiomers have not been detected in each compound.

Monitoring of Reactions. Monitoring of reactions via determination of α-ketoglutarate was done as follows. To 2.5 mL of Tris buffer (0.1 M, pH 8.0) in a cuvette was added 50 μL of NH_4OAc (9.84 g/10 mL), 30 μL of NADH (12 mM), 10 μL of EDTA (10 mg of EDTA–$Na_2H_2{\cdot}2H_2O$/mL), 50 μL of ADP (0.1 M), and 20 μL of GluDH solution (3.4 mg/mL). The mixture was allowed to stand for 3 min for equilibration. The α-hydroxy acid reaction solution[13] (200 μL) was then added to the mixture, and the decrease of NADH concentration was determined at 340 nm.

Preparative Synthesis. Oxidation of diols to their respective α-hydroxy acids was carried out in a 200-mL solution containing α-ketoglutarate monoammonium salt (0.1 M, pH 8.0), racemic diol (0.2 M), NAD (0.1 mM), dithiothreitol (2 mM), and HLADH/AldDH/GluDH (2 mg/12 mg/3.4 mg) coimmobilized in polyacrylamide gels.[14] The reaction pH was controlled automatically at 8.0 by addition of a 1.0 M NaOH solution, and the reaction progress was monitored enzymatically via determination of the concentration of α-ketoglutarate. After 40% conversion, the reaction mixture was centrifuged and the enzyme suspension was washed 3 times with water. The washings and the original reaction solution were combined and extracted continuously with ether to remove unreacted starting material. The aqueous solution was then acidified with concentrated H_2SO_4 and concentrated to 70 mL. Isolation of product through continuous ether extraction for 12 h resulted in 30–35% yield (12–14 mmol) on the basis of

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racemic diols. The turnover numbers and the enzyme activity recovered at the conclusion of reactions are NAD, 800; HLADH, 10^8 (90–92%); AldDH, 10^7 (84–86%); GluDH, 10^8 (90–91%). The ^{1}H NMR data of compounds **3a–h** and their melting points are as follows. Compound **3a**: δ ($CDCl_3$) 4.0 (d, 2 H, methylene), 4.57 (m, 1 H, methine), 9.0–11.0 (OH, exchangeable with D_2O). Compound **3b**: mp 87–88 °C; δ ($CDCl_3$) 4.73 (dd, 2 H, J_{CHF} = 48 Hz, J_{CHCH} = 3.6 Hz), 5.3 (m, 1 H, methine). Compound **3c**: mp 88–89 °C; δ ($CDCl_3$) 3.86 (d, 2 H, methylene), 4.55 (m, 1 H, methine), 9.0–11.0 (br, OH, exchangeable with D_2O). Compound **3d**: δ ($CDCl_3$) 3.60 (d, 2 H, methylene), 4.55 (m, 1 H, methine), 9.0–11.0 (br, OH, exchangeable with D_2O). Compound **3e**: δ ($CDCl_3$) 1.56 (d, 3 H, CH_3), 4.50 (m, 1 H, methine), 9.0–11.0 (br, OH, exchangeable with D_2O). Compound **3f**: δ (D_2O) 4.24 (dd, 1 H, J_{C2-H} = 7.6 and 4.8 Hz), 3.40 (dd, 1 H, J_{C3-H} = 13.0 and 4.8 Hz), 3.08 (dd, 1 H, J_{C3-H} = 13.0 and 7.6 Hz), other ^{1}H exchangeable with D_2O; mp 199–201 °C. Compound **3g**: δ ($CDCl_3$) 4.8 (dd, 1 H, J_{C2-H} = 7.0, 2.0, and 1.5 Hz), 5.21 (m, 1 H, C4-H), 5.26 (m, 1 H, C4-H), 5.96 (ddd, 1 H, J_{C3-H} = 17.0, 10.0, and 7.0 Hz); bp 128–130 °C (23 mmHg). Compound **3h**: δ ($CDCl_3$) 1.01 (t, 3 H, CH_3), 1.92 (m, 2 H, CH_2), 4.51 (t, 1 H, methine). These constants are essentially consistent with those reported previously.[15]

(*R*)-(+)-α-Methoxy-α-(Trifluoromethyl)phenylacetyl (MTPA) Derivatives of the Methyl Esters of Compounds 3c, 3e, and 3h. The MTPA derivatives were prepared according to the procedures described previously.[4] The intensities of the resonances due to the methoxy protons of the diastermers prepared from racemic **3c**, **3e**, and **3h** (prepared by $NaBH_4$ reduction of the corresponding keto species) and the diastereomers produced from the enzymatic reactions were compared: δ ($CDCl_3$) 3.68 for D-**3c** and 3.63 for L-**3c**; 3.65 for D-**3e** and 3.60 for L-**3e**; 3.62 for L-**3h** and 3.56 for D-**3h**.

Oxidation of Amino Alcohols. For the oxidation of amino alcohols, the same enzymes were used except that the cofactor regeneration system was changed: GluDH/α-ketoglutarate was replaced with cyclohexanone which would oxidize NADH under HLADH catalysis. The amino aldehydes produced in the reaction were transformed in situ to amino acids from which the optical purity was determined. After the reaction was completed, the solution was adjusted to pH 12 with NaOH and extracted continuously with chloroform to remove cyclohexanol and unreacted starting material. The aqueous solution containing enzyme product was concentrated to about 10 mL. After addition of ethanol (50 mL) to the mixture, the amino acid was precipitated as sodium salt which was characterized with ^{1}H NMR, and the spectrum was identical with that of authentic L-serine obtained from Aldrich. The optical purity of compound **3f** was determined to be 96% on the basis of the enzymatic procedures described.

(15) See ref 3. Also, the NMR data of compound **3f** and **3g** are consistent with those reported before: Shimohigashi, Y.; Waki, M.; Izumiya, N. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 949. Appelbaum, J.; Stubbe, J. *Biochemistry* **1975**, *14*, 3908. Some other compounds were made before with no NMR data. Compound **3a**: Wohl, A.; Schellenberg, R. *Chem. Ber.* **1922**, *55*, 1404. Compound **3b**: Gottwald, L. K.; Kum, E. *J. Org. Chem.* **1965**, *30*, 877–879. Compound **3d**: Baer, E.; Robinsen, R. *Can. J. Biochem.* **1971**, *49*, 3005. Compound **3h**: Lindstrom, L. A. *Carbohydr. Res.* **1979**, *69*, 269.

Base-Catalyzed Hydroperoxy Keto Aldehyde Cyclization

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Quinghaosu (**1**),[1] one of the most active antimalarials known,[2] offers a potential new pharmacophore in the unique *endo*-peroxide acetal. Schmid and Hofheinz[3] formed this unit by acid-catalyzed cyclization of a key hydroperoxy keto acetal (**2**) which was produced in an elegant though specialized sequence. A more general route to *endo*-peroxide acetals might be available through the cyclization of hydroperoxy keto aldehydes. These might be obtained by the ozonolysis of allylic hydroperoxides (e.g., **3–5**), which are themselves the product of an ene reaction with singlet oxygen. Unfortunately, allylic alcohols undergo "abnormal ozonolysis"[4] in which both of the olefinic carbon atoms are lost, and it may be anticipated that allylic hydroperoxides will behave similarly. This problem, which must be overcome if the synthesis of hydroperoxy keto aldehydes is to succeed, was circumvented by carrying out the ozonolysis on the derived hydroperoxide *tert*-butyldimethylsilyl ether.

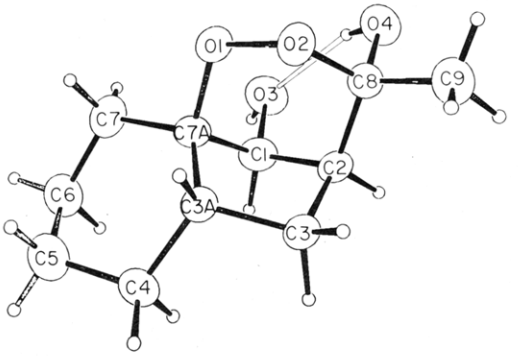
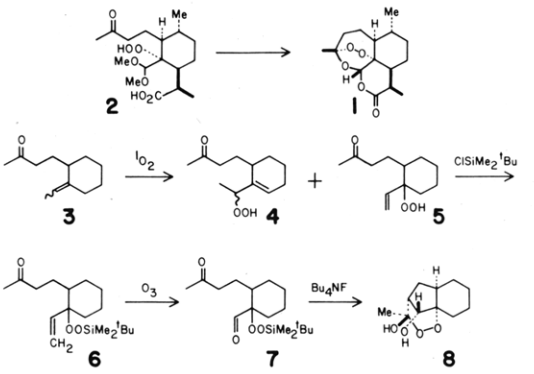


Figure 1. ORTEP plot of the bicyclic *endo*-peroxide.

Scheme I



Keto olefin **3** was available from the action of ethylidenetriphenylphosphorane[5] on methyl 3-(2-oxocyclohex-2-yl)propionate[6] followed by hydrolysis and treatment of the resulting carboxylic acid with methyllithium.[7] Singlet oxygen reacted with **3** to give the unstable allylic hydroperoxide **5** in 81% yield and a compound tentatively identified as its alternate regioisomer **4** in 15% yield. The ^{13}C NMR spectra of **5** and its derived silyl ether **6** indicate that they were obtained, at least predominantly, as single diastereomers. Ozonolysis of **5** gave the product of abnormal ozonolysis, 2-(3-oxobutyl)-cyclohexanone, as expected from the forgoing considerations. In contrast, conversion of the hydroperoxide to the

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