(S)-aziridinecarboxylate, 67413-26-7; (S)-(−)-3-(acetylthio)-2-methylpropanoic acid, 76497-39-7; (2R,3R)-*trans*-2,3-epoxy-1-butanol, 58845-50-4; [^{3}H]methyllithium, 94751-52-7; [3-^{3}H]-3-methyl-1,2-butanediol, 94751-53-8; potassium (R)-[3-^{3}H]isobutyrate, 94751-54-9; potassium (S)-[3-^{3}H]isobutyrate, 94751-55-0; methyl trifluoromethanesulfonate, 333-27-7; benzyl *N*-benzoyldehydroalanine, 94751-56-1; sodium [1-^{14}C]methacrylate, 80631-56-7; sodium [1-^{14}C]isobutyrate, 6917-21-1; sodium [3,4-^{3}H,1-^{14}C]isobutyrate, 94751-57-2; sodium [2-^{3}H,1-^{14}C]isobutyrate, 94751-58-3; (±)-sodium [2-^{3}H,1-^{14}C]-3-mercapto-2-methylpropanoate, 94781-13-2; (±)-sodium [^{35}S,3(R,S)-^{3}H]-3-mercapto-2-methylpropanoate, 94781-14-3; [^{35}S,3(R,S)-^{3}H]-2(R,S)-S-(2-carboxy-*n*-propyl)-L-cysteine, 94751-59-4; [^{35}S]-L-cysteine hydrochloride, 24321-13-9; (E)-[3-^{3}H]-3-bromo-2-methylprop-2-enoic acid, 94751-60-7; β,β′-diiodoisobutyric acid, 50891-94-6.

Enzymes in Organic Synthesis. 34.[1] Preparations of Enantiomerically Pure Exo- and Endo-Bridged Bicyclic [2.2.1] and [2.2.2] Chiral Lactones via Stereospecific Horse Liver Alcohol Dehydrogenase Catalyzed Oxidations of Meso Diols[2]

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Abstract: Preparative-scale horse liver alcohol dehydrogenase catalyzed oxidations of saturated and unsaturated exo- and endo-bridged bicyclic [2.2.1] and [2.2.2] meso diols proceed with complete enantiotopic specificity to give high (64–87%) yields of the corresponding chiral lactones of ≥97% ee. As for previous meso diol oxidations, the stereochemical course of each oxidation (*S*-center CH_2OH oxidation in all cases) is as predicted by the cubic-space model of the active site. An illustration of the asymmetric synthetic value of these chiral lactones is provided by the conversion of one of them into a prostaglandin precursor.

The viability of enzymes as practical chiral catalysts is now well established.[3] In particular, their ability to discriminate between enantiotopic groups of symmetrical substrates such as meso compounds is being exploited to an ever increasing extent in asymmetric synthesis. Horse liver alcohol dehydrogenase (HLADH[4]), a commercially available NAD-dependent alcohol dehydrogenase that catalyzes CH(OH) ⇌ C=O oxidoreductions of a wide range of substrates of organic chemical interest, is one of the most versatile enzymes in this regard. In its oxidative mode, it has been shown to operate stereospecifically on only one of the enantiotopic hydroxyl groups of meso diols possessing acyclic, monocyclic, and bicyclic structures.[5] We have now discovered that the enzyme's remarkable tolerance of structural variations in meso substrates extends to bridged bicyclic compounds. In this paper we report that preparative-scale HLADH-catalyzed oxidations of exo- and endo-bridged bicyclic [2.2.1] and [2.2.2] meso diols proceed with complete enantiotopic specificity to produce enantiomerically pure chiral lactones of asymmetric synthetic value.

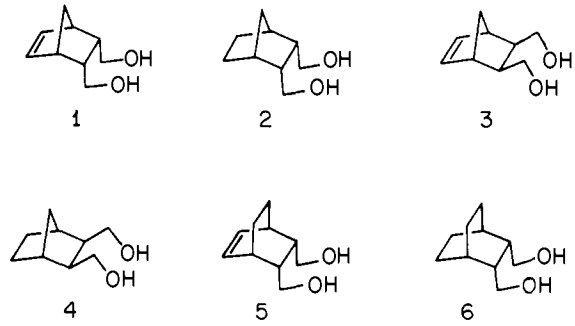
Table I. Relative Rates[a] of HLADH-Catalyzed Oxidations of Diols **1–6**

substrate	rel rate	substrate	rel rate
cyclohexanol	100	**4**	80
1	21	**5**	31
2	22	**6**	25
3	70		

[a] Oxidation rates were measured spectrophotometrically at 25 °C in 0.1 M NaOH–glycine buffer (pH 9) with [S] = 10^{-4} M and [NAD] = 5×10^{-4} M.

Results

Synthesis of Substrates. The substrates evaluated were the meso diols **1–6**. They were prepared by unexceptional routes that are described in full in the Experimental Section.



HLADH-Catalyzed Oxidations of 1–6. The rates of HLADH-catalyzed oxidations of **1–6** relative to that of the standard reference substrate cyclohexanol under the same conditions are recorded in Table I. All of the diols are seen to be good to excellent substrates for which preparative-scale reactions

(1) Part 33. Jones, J. B.; Hinks, R. S.; Hultin, P. G. *Can. J. Chem.*, in press.

(2) Abstracted in part from: Jakovac, I. J. Ph.D. Thesis University of Toronto, 1980. This work was presented in part at the 3rd IUPAC Synthesis Conference, Madison, WI, June 1980.

(3) (a) Suckling, C. J.; Wood, H. C. S. *Chem. Br.* **1979**, *15*, 243. (b) Fischli, A. In "Modern Synthetic Methods"; Scheffold, R., Ed.; Salle/Sauerlander: Frankfurt, 1980; pp 269–350. (c) 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. Jones, J. B. "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic: New York; Vol. 5, in press. (d) Wong, C.-H.; Whitesides, G. M. *Aldrichimica* Acta **1983**, *16*, 27. Findeis, M. A.; Whitesides, G. M. *Annu. Rep. Med. Chem.* **1984**, *19*, 263.

(4) Abbreviations: HLADH, horse liver alcohol dehydrogenase; NAD, nicotinamide adenine dinucleotide, oxidized form; FMN, flavin mononucleotide (riboflavin phosphate); $Eu(tfc)_3$, tris[((trifluoromethyl)hydroxymethylene)-(−)-camphorato]europium(III).

(5) (a) Jakovac, I. J.; Goodbrand, H. B.; Lok, K. B.; Jones, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 4659. (b) Ng, G. S. Y.; Yuan, L.-C.; Jakovac, I. J.; Jones, J. B. *Tetrahedron* **1984**, 1235–1243. (c) Bridges, A. J.; Raman, P. S.; Ng, G. S. Y.; Jones, J. B. *J. Am. Chem. Soc.* **1984**, *106*, 1461. (d) Jones, J. B.; Jakovac, I. J. *Org. Synth.* **1984**, *63*, 10. (e) Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1976**, *98*, 8476. (f) Jones, J. B.; Francis, C. J. *Can. J. Chem.* **1984**, *62*, 2578.

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Scheme I

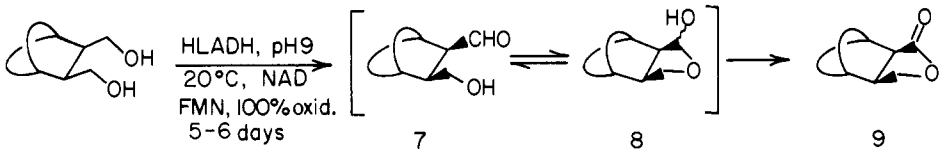
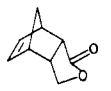
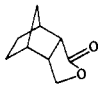
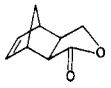
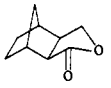
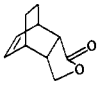
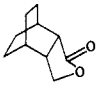


Table II. Results of HLADH-Catalyzed Oxidations of Meso Diols **1–6**[a]

substr	prod[b]	yield, %	ee, %[c]
1	 (+)-(2*S*,3*R*)-**10**	64	>97
2	 (+)-(2*S*,3*R*)-**11**	86	>97
3	 (+)-(2*S*,3*R*)-**12**	74	>97
4	 (+)-(2*S*,3*R*)-**13**	73	>97
5	 (+)-(2*S*,3*R*)-**14**	64	>97
6	 (+)-(2*S*,3*R*)-**15**	87	>97

[a] Reactions carried out under Scheme I conditions. [b] The chiral center descriptors are based on the [2.2.1]heptane and [2.2.2]octane numbering systems. [c] Error limit 3%.[7]

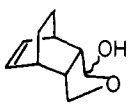
could be undertaken with confidence.

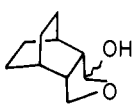
The preparative-scale enzyme-mediated oxidations of **1–6** were carried out at pH 9 using FMN to effect recycling[6] of the catalytic amounts of NAD coenzyme used. The oxidations were performed on up to 1 g of diol and can easily be scaled up if necessary.[5d]

The general reaction pathway followed is summarized in Scheme I. In each case, the oxidations were enantiotopically specific for the hydroxymethyl groups attached to the *S* centers. Under the reaction conditions, the initially formed hydroxyaldehydes **7** underwent further in situ HLADH-promoted oxidation via their hemiacetal forms **8** to yield lactone products **9** directly.

The results of the individual HLADH-mediated oxidations of **1-6** are recorded in Table II.

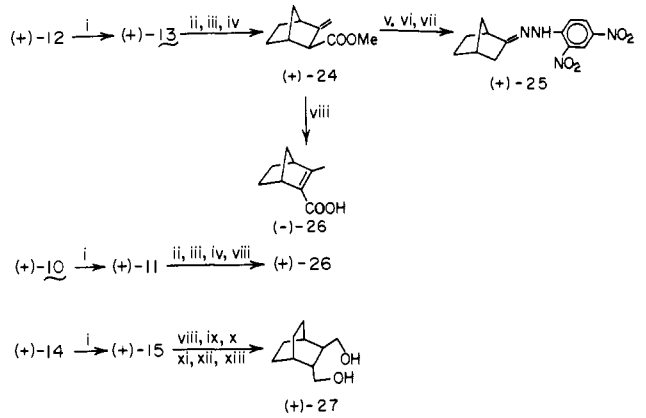
The enantiomerically pure lactone products (+)-**10** to (+)-**15** were isolated directly from the reaction mixtures. In the case of the oxidations of the [2.2.2] diols **5** and **6**, small (10–20%) proportions of the intermediate hemiacetals **16** and **17** were also


16


17

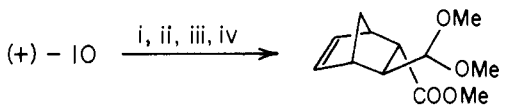
(6) Jones, J. B.; Taylor, K. E. *Can. J. Chem.* **1976**, *55*, 2969.
(7) Jakovac, I. J.; Jones, J. B. *J. Org. Chem.* **1979**, *44*, 2165.

Scheme II[a]



[a] (i) H_2/Pd; (ii) NaSePh; (iii) BF_3Et_2O, MeOH; (iv) H_2O_2; (v) OsO_4, $NaIO_4$; (vi) HCl; (vii) H_2NNH-2,4-$(NO_2)_2Ph$; (viii) KOH; (ix) CH_2N_2; (x) H^+, DHP; (xi) NaOMe; (xii) $LiAlH_4$; (xiii) H_3O^+.

Scheme III[a]



28

[a] (i) KOH; (ii) CH_2N_2; (iii) PCC; (iv) H^+, MeOH.

present. However, these were readily converted into the corresponding optically pure lactones (−)-**14** and (+)-**15**, respectively, by treatment with silver carbonate on Celite.[8]

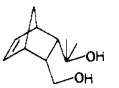
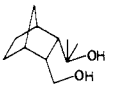
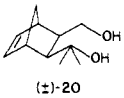
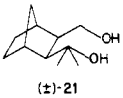
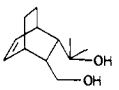
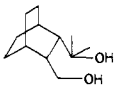
Enantiomeric Excess Determinations. The ee's of the Table II lactones **10–15** were established by their treatment with methyllithium followed by ^1H NMR examination of the diols **18–23** obtained in the presences of $Eu(tfc)_3$.[7] The peak separations observed for the diasterotopic methyl proton resonances of the reference diols (±)-18 to (±)-**23** (obtained from the racemic lactones (±)-**10** to (±)-**15**) are recorded in Table III. No such peak separations were observable under the same conditions in the spectra of **18-23** derived from the enzymically produced lactones.

Absolute Configuration Determinations of 10–15. The absolute configurations of the saturated lactones (+)-**11**, (+)-**13**, and (+)-**15** were established by their degradations to (+)-**26** and the known compounds (+)-**25**[9] and (+)-**27**[10] by the pathways summarized in Scheme II. The rotation of (+)-**25** observed was very close to the predicted[5e] maximum for this compound. The absolute configuration of (+)-**24** then followed from its opposite sign of rotation of the (−)-**24** sample obtained from (+)-**22**. The configurations of the unsaturated lactones (+)-**10**, (+)-**12**, and (+)-**14** were determined by their hydrogenation to (+)-**11**, (+)-**13**, and (+)-**15**, respectively.

The chiral-synthon utility of lactones such as (+)-**10** to (+)-**15** was demonstrated by the conversion of (+)-**10** in four steps and

(8) Fetizon, M.; Golfier, M. *C. R. Hebd. Seances Acad Sci.* **1968**, *267*, 900.
(9) Agosta, W. *J. Am. Chem. Soc.* **1964**, *86*, 2638.
(10) (a) Dang, T. P.; Poulin, J. C.; Kagan, H. B. *J. Organomet. Chem.* **1975**, *91*, 105. (b) Collet, A.; Orienne, M. J.; Jacques, J. *Bull. Soc. Chim. Fr.* **1977**, 494.

Table III. Enantiomeric Shift Differences for Diastereotopic Methyl Groups of Diols (±)-**16** to (±)-**21**

lactone	diol[a]	ppm[b]
(±)-**10**	 (±)-**18**	0.12
(±)-**11**	 (±)-**19**	0.12
(±)-**12**	 (±)-**20**	0.12
(±)-**13**	 (±)-**21**	0.07
(±)-**14**	 (±)-**22**	0.10
(±)-**15**	 (±)-**23**	0.23

[a] Obtained by treatment of precursor lactone with methyllithium. [b] Between *gem*-dimethyl protons in presence of 0.2–0.4 equiv of Eu(tfc)$_3$.

42% overall yield to the prostaglandin precursor (+)-**28**,[11] as shown in Scheme III.

Discussion

The preparative-scale HLADH-catalyzed oxidations were performed on ~1 g of substrate. Scaling up of the reaction to 10 g or more presents no problem.[5d] Each diol **1–6** was a good substrate (Table I) with the reactions proceeding as indicated in Scheme I to yield the enantiomerically pure lactones (+)-**10** to (+)-**15** directly. All lactone yields were routinely good and could be improved further by optimizing the reaction conditions.[5d] Only for the oxidations of the [2.2.2] diols **5** and **6** were any of the intermediate hemiacetals **16** and **17** detectable. However, even in these cases, the final yields of lactones were not affected since **16** and **17** were readily and quantitatively oxidizable to (+)-**14** and (+)-**15**, respectively. The lactones (+)-**14** and (+)-**15** isolated directly from the enzymic reaction medium, and from chemical oxidation of the intermediate hemiacetals **16** and **17**, were both enantiomerically pure and identical in all respects. This establishes that the stereochemical outcome of the HLADH-catalyzed oxidations of the diols **1–6** is determined in the initial step, with the hydroxymethyl groups attached to the *S* centers being oxidized exclusively in each case. The *S*-center preference of the enzyme in its oxidation of meso diols is thus remarkably constant over a very broad spectrum of substrate structures.[5]

The bridged bicyclic lactones producible by this approach extend still further the already considerable[5] range of attractive chiral lactone synthons to which the use of HLADH provides ready access. The general asymmetric synthetic utility of such lactones has already been demonstrated.[5a,b,12] A further specific illustration of the value of the current series of lactones is provided by the conversion of (+)-**10** into the prostaglandin intermediate **28**.[11]

Cubic Active-Site Section Analysis of Stereospecificity. All of the stereochemical results of the HLADH-catalyzed oxidations of meso diols **1–6** are in accord with the predictions of the cubic-space active-site model.[13] The analysis summarized for the [2.2.2] diol **6** in Figure 1 is representative. The analyses in the [2.2.1] series are carried out in a similar manner and are very similar to those outlined for their oxa analogues.[5f] In all cases, oxidation in specific for the CH_2OH group attached to the *S* center. The incomplete oxidations of the hemiacetals in the [2.2.2] series are due to the fact that all hemiactal orientations intrude to a greater or lesser extent into nonallowed space. Intrusions into limited, and toward forbidden, regions are also found for the [2.2.1] hemiacetals.[15] None of these less favorable interactions

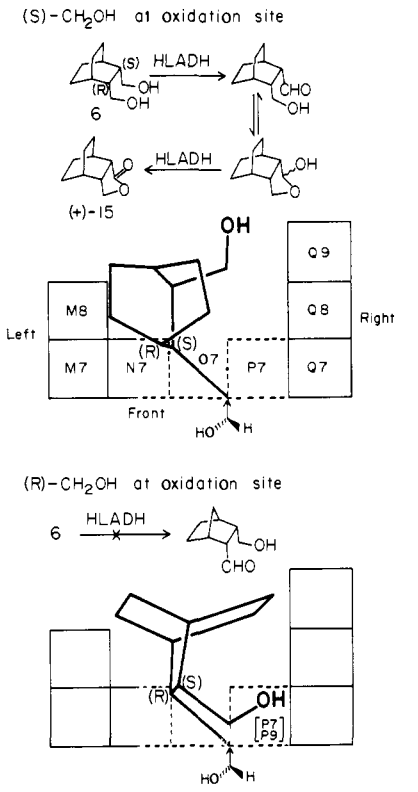


Figure 1. Cubic active-site section analysis of the stereospecificity of HLADH-catalyzed oxidation of the [2.2.2] diol **6**. The model, the alpha-numeric descriptors of the cube locations, and the analytical procedure employed are as described previously.[13] The substrate orientations in this analysis are depicted from the top elevation[13] perspective. Cubes bounded by solid lines are "forbidden" regions where the presence of the coenzyme or amino acid residues of the enzyme preclude accommodation of the substrate. The space above, underneath, and in front of the defined active-site region are forbidden for the same reasons. Substrate binding in cubes bordered by broken lines is "limited" by the proximity of these spaces to forbidden regions. Substrates can locate in limited space but the binding is not favored. Violation of two limited regions becomes equivalent to a forbidden interaction. The open areas are "allowed" regions where the substrate can be freely accommodated. For oxidation to occur, the hydroxyl group must locate at the oxidation site, identified by →. For primary alcohols, HLADH-catalyzed oxidation requires abstraction of the *pro-R* hydrogen atom,[13,14] thereby ensuring a unique CH_2OH orientation. The substrate orientations shown are the most favorable in (a) and the least unfavorable in (b). In (a), for oxidation of the CH_2OH group attached to the *S* center, all of the substrate can locate in allowed regions and oxidation proceeds readily. In (b), no orientations are possible that do not involve unfavorable interactions. In the least unfavorable fit shown, the penetration of limited regions P7 and P9 cannot be avoided. Furthermore, these regions are hydrophobic and the location of a polar hydroxyl group here would be particularly unpropitious. Productive ES complex formation is therefore precluded and oxidation does not occur.

(11) Jones, G.; Raphael, R. A.; Wright, S. *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1676.
(12) Jones, J. B.; Finch, M. A. W.; Jakovac, I. J. *Can. J. Chem.* **1982**, *60*, 2007.
(13) Jones, J. B.; Jakovac, I. J. *Can. J. Chem.* **1982**, *60*, 19.
(14) Donninger, C.; Ryback, G. *Biochem. J.* **1964**, *91*, 11P. Gerlach, H.; Zagalak, B. *J. Chem. Soc., Chem. Commun.* **1973**, 274.
(15) The general approach to cubic section analysis of hemiacetal oxidations is described in ref 5b.

are severe enough to prevent the enzymic oxidation of any hemiacetal intermediate, although, as a consequence, the rate of each reaction is slowed considerably at the hemiacetal oxidation stage. In fact, it is the slow hemiacetal oxidation step that is largely responsible for the several-day reaction periods needed for lactone formation. Product inhibition may also be a factor. The rates of oxidation of the diols **1–6** themselves are so high (Table I) that the reactions would be over in a few hours if the initial transformations were rate determining.

Experimental Section

NAD was obtained from Kyowa Hakko Kojyo, New York, and FMN and HLADH (EC 1.1.1.1, 1× crystallized) from Sigma. The activity of each batch of enzyme was assayed[16] prior to use. Unless specified otherwise, IR spectra were measured on films (for liquids) or on $CHCl_3$ solutions (for solids) and ^1H NMR spectra on $CDCl_3$ solutions. All instrumentation, purification, and anlytical procedures used were as described previously.[5a] Boiling points are of Kugelrohr distillations.

Preparations of Meso Diols 1–6. *cis-endo*-2,3-Bis(hydroxymethyl)-bicyclo[2.2.1]hept-5-ene (1). *cis-endo*-Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid anhydride (8.2 g, 0.05 mol, prepared by the method of Craig[17]) was reduced with $LiAlH_4$ to give *cis-endo*-2,3-bis(hydroxymethyl)bicyclo[2.2.1]hept-5-ene (**1**, 6.34 g, 82% yield): mp 78–80 °C (lit.[18] mp 85–86 °C); ^1H NMR δ 1.40 (t, 2 H, J = 1 Hz), 2.50 (m, 2 H), 3.10–3.70 (m, 4 H), 4.10 (br s, 2 H), 6.00 (t, 2 H, J = 1 Hz).

***cis-endo*-2,3-Bis(hydroxymethyl)bicyclo[2.2.1]heptane (2).** The above diol **1** (3.0 g, 19.5 mmol) in 95% aqueous EtOH (30 mL) containing 5% Pd on C (100 mg) was hydrogenated under H_2 (1 atm) to give *cis-endo*-2,3-bis(hydroxymethyl)bicyclo[2.2.1]heptane (**2**, 2.79 g, 92% yield): bp 100 °C (0.1 mmHg), mp 63–64 °C (lit.[18] mp 65–66 °C); ^1H NMR δ 1.38 (br s, 6 H), 2.24 (m, 4 H), 3.38–4.18 (m, 4 H), 4.68 (br s, 2 H).

***cis-exo*-2,3-Bis(hydroxymethyl)bicyclo[2.2.1]hept-5-ene (3).** *cis-exo*-Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid anhydride (3.0 g, 18.3 mmol, obtained from the endo isomer by heat isomerization) was reduced with $LiAlH_4$ to give *cis-exo*-2,3-bis(hydroxymethyl)bicyclo[2.2.1]hept-5-ene (**3**, 2.5 g, 89% yield): pb 120 °C (0.1 mmHg) [lit.[18] bp 114–116 °C (0.6 mmHg)]; ^1H NMR δ 1.30 (m, 2 H), 1.80 (m, 2 H), 2.66 (m, 2 H), 3.74 (m, 4 H), 4.18 (br s, 2 H), 6.18 (t, 2 H, J = 2 Hz).

***cis-exo*-2,3-Bis(hydroxymethyl)bicyclo[2.2.1]heptane (4).** Hydrogenation of the above diol **3** (2.5 g, 16.2 mmol, as for **12**) yielded *cis*-exo-2,3-bis(hydroxymethyl)bicyclo[2.2.1]heptane (**4**, 2.4 g, 95% yield: bp 120 °C (0.1 mmHg) (lit.[18] bp 105–107 °C (0.11 mmHg); ^1H NMR δ 0.86–1.70 (m, 6 H), 2.04 (m, 4 H), 3.64 (m, 6 H).

***cis-endo*-2,3-Bis(hydroxymethyl)bicyclo[2.2.2]oct-5-ene (5).** *cis-endo*-Bicyclo[2.2.2]oct-5-ene-2,3-dicarboxlic acid anhydride (5.0 g, 28 mmol, from Aldrich) afforded *cis-endo*-bis(hydroxymethyl)bicyclo-[2.2.2]oct-5-ene (**5**, 3.5, g, 74% yield): mp 96–98 °C (lit.[19] mp 103–103.8 °C); ^1H NMR δ 1.10–1.70 (m, 4 H), 3.40–3.90 (m, 6 H) and 6.10 (m, 2 H).

***cis*-2,3-Bis(hydroxymethyl)bicyclo[2.2.2]octane (6).** Hydrogenation of the above diol **5** (1.5 g, 8.93 mmol, as for **12**) gave *cis*-2,3-bis(hydroxymethyl)bicyclo[2.2.2]octane (**6**, 1.2 g, 79% yield): mp 88–89 °C (lit.[19] mp 89.4–90.2 °C); ^1H NMR δ 1.10–2.42 (m, 12 H), 3.40–4.64 (m, 6 H).

Preparations of Racemic Lactones (±)-10 to (±)-15. Lactones (±)-**10**, -**12**, and -**14**, were obtained in 65–78% yields by reduction of the corresponding anhydrides with $NaBH_4$, using the general method of Bailey and Johnson.[20] Lactones (±)-**11**, -**13**, and -**15** were prepared in 70–99% yield by hydrogenation of **10**, **12**, and **14**, respectively. (±)-*cis-endo*-3-(Hydroxymethyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid lactone ((±)-**10**):[21] mp 120–122 °C; IR ν 1770 cm^{-1}; ^1H NMR δ 1.54 (q, 2 H, J = 10 Hz), 2.90–3.20 (m, 4 H), 3.70–4.50 (m, 2 H), 6.30 (m, 2 H); prepared from *cis-endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid anhydride.[17] (±)-*cis-endo*-3-(Hydroxymethyl)bicyclo[2.2.1]heptane-2-carboxylic acid lactone ((±)-**11**): mp 145–146 °C (lit.[22] mp 148–149 °C); ^1H NMR δ 1.30–1.72 (m, 6 H), 2.30–3.18 (m, 4 H), 4.18–4.36 (m, 2 H); prepared from (±)-**10**. (±)-*cis-endo*-3-(Hydroxymethyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid lactone ((±)-**12**): mp 64–65 °C; IR ν 1770 cm^{-1}; ^1H NMR δ 1.54 (s, 2 H), 2.60 (m, 2 H), 3.30 (br s, 2 H), 3.64–4.70 (m, 2 H), 6.26 (t, 2 H, J = 2 Hz); prepared from *cis-exo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid anhydride.[17] (±)-*cis*-exo-3-(Hydroxymethyl)bicyclo[2.2.1]heptane-2-carboxylic acid lactone ((±)-**13**): bp 120 °C (1 mmHg); IR ν 1770 cm^{-1}; ^1H NMR δ 1.00–1.84 (m, 6 H), 1.96–2.80 (m, 4 H), 3.40–4.84 (m, 2 H); prepared from (±)-**12**. (±)-*cis-endo*-3-(Hydroxymethyl)bicyclo[2.2.2]oct-5-ene-2-carboxylic acid lactone ((±)-**14**): mp 86–88 °C (lit.[23] mp 91–92.5 °C); IR ν 177 cm^{-1}; ^1H NMR δ 1.40 (m, 4 H), 2.50–3.20 (m, 4 H), 3.62–4.54 (m, 2 H) and 6.30 (t, 2 H, J = 5 Hz); prepared from *cis-endo*-bicyclo-[2.2.2]oct-5-ene-2,3-dicarboxylic acid anhydride (from Aldrich). (±)-*cis*-3-(Hydroxymethyl)bicyclo[2.2.2]octane2-carboxylic acid lactone ((±)-**15**): mp 146–147 °C (lit.[24] mp 136–138 °C); IR ν 1770 cm^{-1}; ^1H NMR δ 1.00–1.84 (m, 9 H), 2.06 (m, 1 H), 2.64 (m, 2 H) and 4.00–4.62 (m, 2 H); prepared from (±)-**14**.

HLADH-Catalyzed Oxidations. The initial rates of oxidation of **1–6** under kinetic assay conditions, relative to that of the standard reference substrate, cyclohexanol, were determined by the general assay method of Dalziel[16] as described previously.[5a] The results are recorded in Table I.

Preparative-Scale Oxidations of Diols 1–6. Oxidation of Meso Diol 1 to the (+)-(2*S*,3*R*)-Lactone 10. *cis-endo*-2,3-Bis(hydroxymethyl)bicyclo[2.2.1]hept-5-ene (**1**, 1.0 g, 6.5 mmol), NAD^+ 720 mg, 1.1 mmol), and FMN (9.72 g, 20.3 mmol) were dissolved in 0.1 M glycine-NaOH buffer (pH 9, 150 mL) at room temperature (20 °C) and the pH adjusted to 9 with 15% aqueous NaOH. HLADH (40 mg) was then added and the mixture kept at room temperature for 6 days, with periodic adjustment of the pH to 9 with 15% aqueous NaOH. The mixture turned from its initial clear orange to an opaque, almost-black color as the reaction proceeded. The course of the oxidation was monitored by GLC analysis of $CHCl_3$ extracts of small aliquots. When the reaction was complete (6 days), the pH was brought to 3 with 2 M hydrochloric acid and the mixture continuously extracted with $CHCl_3$ (12 h). The dried ($MgSO_4$) extract was rotoevaporated and then chromatographed on silica gel (20 g). Elution with EtOAc/hexane (1:10) gave (+)-(2*S*,3*R*)-*cis*-endo-3-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid lactone[25] ((+)-**10**, 620 mg, 64% yield, 100% ee), mp 120–122 °C. $[\alpha]^{25}_D$ +143.2° (*c* 5.2, $CHCl_3$), spectral data identical with (±)-**10**.

The oxidations of the other diols **2–6** were carried out using similar procedures, with the following results:

Oxidation of Meso Diol 2 to the (+)-(2*S*,2*R*)-Lactone 11. Oxidation of *cis-endo*-2,3-bis(hydroxymethyl)bicyclo[2.2.1]heptane (**2**, 1.0 g, 6.4 mmol) for 6 days gave (+)-(2*S*,3*R*)-*cis-endo*-3-(hydroxymethyl)bicyclo[2.2.1]heptane-2-carboxylic acid lactone ((+)-**11**, 835 mg, 86% yield, 100% ee), mp 145–146 °C, $[\alpha]^{25}_D$ +123.7° (*c* 0.84, $CHCl_3$), spectral data as for (±)-**11**. Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.17; H, 8.02%.

Oxidation of Meso Diol 3 to the (+)-(2*S*,3*R*)-Lactone 12. Oxidation of *cis-exo*-2,3-bis(hydroxymethyl)bicyclo[2.2.1]hept-5-ene (**3**, 600 mg, 3.9 mmol) for 5 days yielded (+)-(2*S*,3*R*)-*cis,exo*-3-(hydroxymethyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid lactone[25] ((+)-**12**, 435 mg, 74% yield, 100% ee), pb 100 °C (1 mmHg), mp 64–65 °C, $[\alpha]^{25}_D$ +127.8° (*c* 4.35, $CHCl_3$), spectral data as for (±)-**12**.

Oxidation of Meso Diol 4 to the (+)-(2*S*,3*R*)-Lactone 13. Oxidation of *cis-exo*-2,3-bis(hydroxymethyl)bicyclo[2.2.1]heptane (**4**, 850 mg, 5.45 mmol) for 5 days afforded (+)-(2*S*,3*R*)-*cis-exo*-3-(hydroxymethyl)bicyclo[2.2.1]heptane-2-carboxylic acid lactone[25] ((+)-**13**, 607 mg, 73% yield, 100% ee), bp 100 °C (1 mmHg), $[\alpha]^{25}_D$ +89.8° (*c* 0.6, $CHCl_3$), spectral data as for (±)-**13**.

Oxidation of Meso Diol 5 to the (+)-(2*S*,3*R*)-Lactone 14. Oxidation of *cis-endo*-2,3-bis(hydroxymethyl)bicyclo[2.2.2]oct-5-ene (**5**, 900 mg, 5.4 mmol) for 5 days gave (+)-*cis-endo*-3-(hydroxyethyl)bicyclo-[2.2.2]oct-5-ene-2-carboxylic acid lactone ((+)-**14**, 390 mg, 44% yield, 100% ee), mp 86–88 °C, $[\alpha]^{25}_D$ +92.0° (*c* 3.9, $CHCl_3$), spectral data as for (±)-**14**. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.36. Found: C, 73.06; H, 7.42%. The precursor hemiacetal **16** (180 mg, 20% yield), $[\alpha]^{25}_D$ +91.8° (*c* 1, $CHCl_3$), was also isolated. On oxidation with silver carbonate on Celite,[8] it yielded (+)-**14** identical in all respects with (+)-**10** obtained by direct enzyme-catalyzed oxidation. The total yield of (±)-**14** was 560 mg (62%).

Oxidation of Meso Diol 6 to the (+)-(2*S*,3*R*)-Lactone 15. Oxidation of *cis*-2,3-bis(hydroxymethyl)bicyclo[2.2.2]octane (**6**, 800 mg, 4.7 mmol) for 5 days yielded (+)-(2*S*,3*R*)-*cis*-3(hydroxymethyl)bicyclo[2.2.2]octane-2-carboxylic acid lactone ((+)-**15**, 630 mg, 81% yield, 100% ee), mp 146–147 °C, $[\alpha]^{25}_D$ +113° (*c* 6.2, $CHCl_3$), spectral data as for (±)-**15**.

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Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.98, H, 8.49%. The precursor hemiacetal **17** (50 mg, 7% yield) was also isolated: IR ν 3460 cm^{-1}; ^1H NMR δ 0.70–1.90 (m, 4 H), 2.00–2.92 (m, 4 H), 3.30–4.20 (m, 3 H), 4.98 (s, 1 H), 5.88–6.34 (m, 2 H). On oxidation with silver carbonate on Celite,[8] it gave enantiomerically pure (+)-**15**. The total yield of (+)-**15** was 676 mg (87%).

Enantiomeric Excess Determinations. The ee's of the lactones (+)-**10** to (+)-**15** were determined by reacting each with excess MeLi and examining the ^1H NMR spectra of the resulting diols **18–23** in the presence of 0.2–0.4 equiv of $Eu(tfc)_3$.[7] $\Delta\Delta\delta$ separations of 0.07–0.23 ppm (Table II) were observed for the reference diols obtained from the corresponding racemic lactones. Only one enantiomer was detectable in the diols from the enzyme-derived lactones within the error limits of the method of ±3%. The properties of the diols (−)-**18** to (−)-**23** are as follows.

(−)-(**2*S*,3*R***)-***cis-endo*-3-(**Hydroxymethyl**)-**2-(2-hydroxypropyl)bicyclo[2.2.1]hept-5-ene** ((−)-**18**, 86% yield): mp 97–98 °C, $[\alpha]^{25}_D$ −4.4° (*c* 3.7, $CHCl_3$); ^1H NMR δ 1.22 (d, 6 H, J = 11 Hz), 1.42 (t, 2 H, J = 1 Hz), 2.34–2.60 (m, 2 H), 2.64–2.88 (m, 2 H), 3.44–3.74 (m, 2 H), 5.36 (s, 2 H), 6.0–6.18 (m, 2 H). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.48; H, 9.95. Found: C, 72.58; H, 9.69%.

(−)-(**2*S*,3*R***)-***cis-endo*-3-(**Hydroxymethyl**)-**2-(2-hydroxypropyl)bicyclo[2.2.1]heptane** ((−)-**19**, quantitative yield): mp 84–85 °C, $[\alpha]^{25}_D$ −12.7° (*c* 2.6, $CHCl_3$); ^1H NMR δ 1.42 (d, 12 H, J = 6 Hz), 1.70–2.52 (m, 4 H), 3.80–4.08 (m, 2 H), 5.00 (s, 2 H). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.93. Found: C, 71.66; H, 11.10%.

(−)-(**2*S*,3*R***)-***cis-exo*-3-(**Hydroxymethyl**)-**2-(2-hydroxypropyl)bicyclo[2.2.1]hept-5-ene** ((−)-**20**, 78% yield) mp 87–88 °C, $[\alpha]^{25}_D$ −37.1° (*c* 0.5, $CHCl_3$); ^1H NMR δ 1.30 (d, 6 H, J = 4 Hz), 1.40–2.00 (m, 4 H), 2.50 (br s, 2 H), 3.76 (d, 2 H, J = 6 Hz), 5.48 (s, 2 H), 6.18 (m, 2 H). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.58; H, 9.95. Found: C, 72.58; H, 9.69%.

(−)-(**2*S*,3*R***)-***cis-endo*-3-(**Hydroxymethyl**)-**2-(2-hydroxypropyl)bicyclo[2.2.1]heptane** ((−)-**21**, quantative yield): bp 100 °C (0.3 mmHg), $[\alpha]^{25}_D$ −27.9° (*c* 0.66, $CHCl_3$); ^1H NMR δ 0.90–2.20 (m, 10 H), 1.28 (d, 6 H, J = 3 Hz), 3.70 (m, 2 H), 5.58 (s, 2 H). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.93. Found: C, 71.48; H, 10.72%.

(−)-(**2*S*,3*R***)-***cis-endo*-3-(**Hydroxymethyl**)-**2-(2-hydroxypropyl)bicyclo[2.2.2]oct-5-ene** ((−)-**22**, quantative yield: mp 43–44 °C, $[\alpha]^{25}_D$ −22.74° (*c* 1, $CHCl_3$); ^1H NMR δ 1.24 (d, 6 H, J = 10 Hz), 1.30–2.72 (m, 8 H), 3.48–3.82 (m, 2 H), 5.70 (br s, 2 **H**), 5.98–6.32 (m, 2 H). Anal. Calcd for $C_{10}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.32; H, 10.54%.

(−)-(**2*S*,3*R***)-***cis*-3-(**Hydroxymethyl**)-**2-(2-hydroxypropyl)bicyclo-[2.2.2]octane** ((−)-**23**, quantative yield): bp 120 °C (1 mmHg), $[\alpha]^{25}_D$ −71.3° (*c* 1.2, $CHCl_3$); ^1H NMR δ 1.30 (d, 6 H, J = 5 Hz), 1.58 (br s, 12 H), 3.40–4.22 (m, 2 H), 4.92 (br s, 2 H). Anal. Calcd for $C_{10}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.93; H, 11.54%.

Absolute Configuration Determinations. The correlations are summarized in Scheme II. (+)-(**2*S*,3*R***)-***cis-exo*-3-(**Hydroxymethyl**)**bicyclo[2.2.1]heptane-2-carboxylic Acid Lactone** ((+)-**13**). By the general procedure of Liotta and Santiestaban,[26] Na (382 mg, 16.6 mmol) was added to a solution of diphenyl diselenide (2.36 g, 7.57 mmol) in THF (15 mL) and the mixture refluxed under N_2 for 4 h. HMPA (0.2 mL), followed by the lactone (+)-**13** (2.3 g, 15 mmol), was then added and the mixture was refluxed for a further 4 h. The cooled solution was diluted with MeOH (10 mL) followed by water (50 mL), and the basic solution washed with ether (3 × 25 mL). The aqueous layer was acidified with 6 M hydrochloric acid and extracted with ether (3 × 30 mL). The ether extracts were washed with water (50 mL) and then with saturated aqueous $NaHCO_3$ (2 × 50 mL) and dried ($MgSO_4$). Rotoevaporation gave a viscous oil that was reluxed in MeOH (50 mL) containing $BF_3{\cdot}Et_2O$ (2.50 g, 17.6 mmol) for 16 h. The mixture was concentrated, diluted with water (20 mL), and extracted with ether (3 × 20 mL). The ether extract was washed with water (2 × 25 mL) and then with saturated aqueous $NaHCO_3$ (2 × 25 mL) and dried ($MgSO_4$). Rotoevaporation gave methyl (+)-(2*S*,3*R*)-*cis-exo*-3-[(phenylselenyl)methyl]bicyclo[2.2.1]heptane-2-carboxylate (3.2 g) as a yellow-orange oil: $[\alpha]^{25}_D$ +45.6° (*c* 1, $CHCl_3$); IR ν 1736 cm^{-1}; ^1H NMR δ 0.90–3.04 (m, 12 H), 3.60 (s, 3 H), 7.10–7.60 (m, 5 H).

To this selenide (3.2 g, 9.9 mmol) in THF (100 mL) containing $MgSO_4$ (5 g) at 20 °C was added dropwise 30% aqueous H_2O_2 (11.1 mL, 99 mmol). When the H_2O_2 addition was complete, the mixture began to reflux spontaneously. This subsided after 10 min, after which time the bright yellow color had faded considerably. The mixture was stirred at 20 °C for 12 h, and enough water was added to dissolve the $MgSO_4$. The aqueous solution was extracted with ether (2 × 50 mL), and the ether extracts were washed with water (50 mL) and then with saturated aqueous NaCl (50 mL). The dried ($MgSO_4$) ether solution was evaporated and then Kugelrohr distilled to give methyl (+)-(2*S*)-*exo*-3-methylenebicyclo[2.2.1]heptane-2-carboxylate[27] ((+)-**24**, 1.01 g, 62% yield): bp 100 °C (15 mm Hg), $[\alpha]^{25}_D$ +90.0° (*c* 1, $CHCl_3$); IR ν 1736 cm^{-1}; ^1H NMR δ 1.04–1.96 (m, 6 H), 2.50–2.78 (m, 2 H), 2.78–2.96 (m, 1 H), 3.60 (s, 3 H), 4.92 (d of d, 2 H, J = 6 Hz).

The β,γ-unsaturated ester (+)-**24** (900 mg, 5.4 mmol) was added to OsO_4 (50 mg) in a mixture of ether (10 mL) and water (10 mL) at 20 °C.[28] To the black mixture was then added Na metaperiodate (2.9 g, 13.6 mmol) in small portions during 30 min. The mixture was stirred at 20 °C for 16 h, saturated aqueous Na bisulfite (5 mL) added, and the whole extracted with ether (3 × 10 mL). The ether extracts were washed with 10% aqueous sodium thiosulfate (3 × 10 mL), then dried ($MgSO_4$), and rotoevaporated to give methyl (+)-(2*S*)-*exo*-bicyclo[2.2.1]heptane-3-one-2carboxylate (700 mg, 78% yield) $[\alpha]^{25}_D$ +44.5° [*c* 1, $CHCl_3$]; IR ν 1730 cm^{-1}; ^1H NMR δ 1.20–2.44 (m, 6 H), 2.64–3.30 (m, 3 H), 3.78 (s, 3 H). This keto ester (124 mg, 0.74 mmol) in 12 M hydrochloric acid (6 mL) was refluxed for 5 h and then cooled, diluted with water (100 mL), and extracted with ether (5 × 20 mL). The ether extracts were washed successively with water (2 × 20 mL), 15% aqueous NaOH (2 × 20 mL), and saturated aqueous NaCl (2 × 20 mL) and then dried ($MgSO_4$). The ether was removed by careful distillation at 760 mmHg through a 38-cm Vigreux column. The norbornanone residue (55 mg, 67% yield) was treated with a warm solution of (2,4-dinitrophenyl)-hydrazine (118 mg, 0.59 mol) in MeOH 6 mL) containing 12 M hydrochloric acid (0.5 mL). The mixture was then cooled and the orange crystals were filtered off to give (+)-(1*S*)-bicyclo[2.2.1]heptan-2-one (2,4-dinitrophenyl)hydrazone ((+)-**25**, 80 mg, 37% yield from keto ester percursor) that after recrystallization from EtOH had mp 128.5–129 °C: $[\alpha]^{25}_D$ +50.2° (*c* 0.43, $CHCl_3$) (lit.[9] mp 129–131 °C, $[\alpha]_D$ +30° ($CHCl_3$), lit.[5e] (predicted max) $[\alpha]^{25}_D$ +51.3° ($CHCl_3$)); ^1H NMR δ 1.20–1.94 (m, 6 H), 2.10–2.36 (m, 2 H), 2.56–2.84 (m, 1 H), 2.94–3.14 (m, 1 H), 7.88 (d, 1 H, J = 10 Hz), 8.26 (d of d, 1 H, J = 2 Hz), 9.06 (d, 1 H, J = 2 Hz), 10.66 (br s, J = 1 Hz).

(+)-(**2*S*,3*R***)-***cis-exo*-3-(**Hydroxymethyl**)**bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid Lactone** ((+)-**12**). The absolute configuration of the unsaturated exo-lactone (+)-**12** (200 mg, 1.33 mmol) was established by its hydrogenation in EtOH containing 5% Pd/C to (+)-(2*S*,3*R*)-*cis-exo*-3-(hydroxymethyl)bicyclo[2.2.1]heptane-2-carboxylic acid lactone ((+)-**13**, 194 mg, 96% yield, $[\alpha]^{25}_D$ +89.0° (*c* 0.83, $CHCl_3$).

(+)-(**2*S*,3*R***)-***cis-endo*-3-(**Hydroxymethyl**)**bicyclo[2.2.1]heptane-2-carboxylic Acid Lactone** ((+)-**11**). As described above for (+)-**13** → (+)-**24**, the lactone (+)-**11** (2.0 g, 13.2 mmol) was converted to methyl (+)-(2*R*)-*endo*-3-methylenebicyclo[2.2.1]heptane-2-carboxylate (323 mg, 15% overall yield): bp 100 °C (15 mmHg), $[\alpha]^{25}_D$ +41.7 (*c* 2, $CHCl_3$); IR ν 1736 cm^{-1}; ^1H NMR δ 1.20–1.80 (m, 6 H), 2.78–2.88 (m, 2 H), 3.18–3.40 (m, 1 H), 3.72 (s, 3 H), 4.94 (d of d, 2 *H*, J = 13 Hz). This material (30 mg, 0.18 mmol) was refluxed in MeOH (2 mL) containing KOH (28 mg, 0.5 mmol) for 16 h. The MeOH was removed by rotoevaporation and the residue dissolved in water (5 mL). The aqueous solution was washed with ether (2 × 25 mL). It was then acidified with 6 M hydrochloric acid and extracted with ether (3 × 5 mL). The ether extract was washed with saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and rotoevaporated to give (+)-(1*R*)-3-methylbicyclo[2.2.1]hept-2-ene-2-carboxylic acid ((−)-**26**, 17 mg, 62% yield): mp 45–49 °C, $[\alpha]^{25}_D$ +88.2° (*c* 0.1, $CHCl_3$); IR ν 3400–2800 (br), 1665, 1622 cm^{-1}; ^1H NMR δ 0.9–3.0 (m, 8 H), 2.16 (s, 3 H), 9.4 (s, 1 H).

This material was spectroscopically identical with a sample of the (−) enantiomer of **26** obtained from (+)-**24** above in the same way. The (−)-**26** obtained had mp 46–49 °C, $[\alpha]^{25}_D$ −88.9° (*c* 0.1, $CHCl_3$) (lit.[29] (±) mp 41–44 °C).

(+)-(**2*S*,3*R***)-***cis-endo*-3-(**Hydroxymethyl**)**bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid Lactone** ((+)-**10**). The absolute configuration of the unsaturated *endo*-lactone (+)-**10** (100 mg, 6.7 mmol) was established as for (+)-**12** → (+)-**13** by its hydrogenation to (+)-(2*S*,3*R*)-*cis-endo*-3-(hydroxymethyl)bicyclo[2.2.1]heptane-2-carboxylic acid lactone ((+)-**11**, 97 mg, 96% yield), $[\alpha]^{25}_D$ +123.0° (*c*, 0.9, $CHCl_3$).

(+)-(**2*S*,3*R***)-***cis*-3-(**Hydroxymethyl**)**bicyclo[2.2.1]octane-2-carboxylic Acid Lactone** ((+)-**15**). The [2.2.2] lactone (+)-**15** (750 mg, 4.52 mmol) was refluxed for 4 h in MeOH (5 mL) containing KOH (308 mg, 5.5 mmol). The MeOH was rotoevaporated and EtOAc added to the solid

(25) Because, inexplicably, satisfactory elemental analyses could not be obtained for this compound, its elemental composition was confirmed by analysis of the diol obtained from the methyllithium reaction used in the ee determination.

(26) Liotta, D.; Santiesteban, H. *Tetrahedron Lett.* **1977**, 4369.

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residue. The mixture was acidified to pH 6 at 0 °C with 2% hydrochloric acid. The ethyl acetate layer was separated and treated with ethereal CH_2N_2 until a yellow color persisted. The solvent was rotoevaporated off and the residue stirred for 18 h at 20 °C in dihydropyran (10 mL) containing toluene-*p*-sulfonic acid (5 mg). Saturated aqueous Na_2CO_3 (10 mL) was then added and the mixture extracted with EtOAc (3 × 10 mL). The EtOAc extracts were dried (K_2CO_3) and evaporated, and the oily residue was chromatographed on silica gel (50 g). EtOAc–hexane (1:20) elution yielded methyl (+)-(2*S*,3*R*)-*cis*-3-[(tetrahydropyranyloxy)methyl]bicyclo[2.2.2]octane-2-carboxylate (489 mg, 38% yield), IR ν 1736 cm^{-1}.

This material (300 mg, 1.06 mmol) was refluxed for 18 h in MeOH (5 mL) containing Na (24 mg, 1.06 mmol). The MeOH was removed by rotoevaporation and the residue dissolved in water (10 mL) and extracted with EtOAc (4 × 10 mL). The EtOAc extracts were washed with saturated aqueous NaCl (2 × 5 mL), dried ($MgSO_4$), and evaporated. The residue was purified by TLC on silica (EtOAc–hexane (1:3) development) to give methyl (+)-(2*S*,3*R*)-*trans*-3-[(tetrahydropyranyloxy)methyl]bicyclo[2.2.2]octane-2-carboxylate (269 mg, 88%): $[\alpha]^{25}_D$ +33.8° (*c* 1, $CHCl_3$); IR ν 1736 cm^{-1}; ^1H NMR δ 1.0–2.70 (m, 18 H), 3.22–4.36 (m, 4 H), 3.72 (s, 3 H), 4.82 (br d, 1 H, *J* = 21 Hz).

This (+)-*trans*-THP ester (260 mg, 0.92 mmol) in THF (2 mL) was added with stirring to $LiAlH_4$ (53 mg, 1.3 mmol) in THF (1 mL) at 20 °C, and stirring was continued for 16 h. The reaction was then quenched by the careful sequential addition of water (0.05 mL), 15% aqueous NaOH (0.05 mL), and water (0.15 mL). The mixture was filtered and the filtrate rotoevaporated. The residue obtained was stirred for 4 h with acetic acid–H_2O–THF (3:1:1, 2 mL). Aqueous NaOH, 15%, was then added until the mixture was basic. It was then extracted with EtOAc (3 × 5 mL). The EtOAc extracts were washed with saturated aqueous NaCl (1 × 5 mL), dried ($MgSO_4$), and evaporated. Kugelrohr distillation of the residue afforded (+)-(2*R*,3*R*)-*trans*-bis(hydroxymethyl)bicyclo[2.2.2]octane ((+)-**27**, 88 mg, 56% yield): bp 130 °C (0.25 mmHg), mp 90–94 °C (lit.[10a] mp 108–110 °C), $[\alpha]^{25}_D$ +50.9° (*c* 1, MeOH), lit.[10b] $[\alpha]^{25}_D$ +53.4° (*c* 1, MeOH); IR ν 3390 cm^{-1}; ^1H NMR δ 1.70 (s, 12 H), 3.30–3.72 (m, 2 H), 4.40 (br s, 2 H).

(+)-(2*S*,3*R*)-*cis*-*endo*-3-(Hydroxymethyl)bicyclo[2.2.2]oct-5-ene-2-carboxylic Acid Lactone ((+)-14). The absolute configuration of the saturated [2.2.2] lactone (+)-**14** (100 mg, 0.61 mmol) was established as for (+)-**12** → (+)-**13** by its hydrogenation to (+)-(2*S*,3*R*)-*cis*-3-(hydroxymethyl)bicyclo[2.2.2]octane-2-carboxylic acid lactone ((+)-**15**, 93 mg, 95% yield), $[\alpha]^{25}_D$ +114.7° (*c* 0.74, $CHCl_3$).

Conversion of Lactone (+)-10 to the Prostaglandin Precursor 28. The [2.2.1] lactone (+)-**10** (1.0 g, 6.7 mmol) was refluxed for 1 h in MeOH (5 mL) containing KOH (560 mg, 10 mmol). The solvent was then rotoevaporated and EtOAc (50 mL) added to the residual white solid. The mixture was cooled to 0 °C, acidified to pH 4 with 2 M hydrochloric acid, and extracted with EtOAc. The EtOAc extracts were treated with ethereal CH_2N_2 until faintly yellow. Excess CH_2N_2 was removed by bubbling N_2 into the solution, which was then dried ($MgSO_4$) and rotoevaporated. The residual oil was dissolved in CH_2Cl_2 (10 mL) at 20 °C and pyridinium chlorochromate (2.02 g, 10 mmol) added with stirring. After 1 h, the mixture was filtered and the solid washed with ether (10 × 5 mL). The combined organic solutions were filtered through a Celite plug and rotoevaporated. The residual oil was diluted with MeOH (20 mL) containing concentrated H_2SO_4 (2 drops) and the mixture refluxed for 36 h and then cooled. Saturated aqueous Na_2CO_3 (50 mL) was added cautiously and the aqueous layer extracted with EtOAc (5 × 15 mL). The dried ($MgSO_4$) EtOAc solution was evaporated and the residue purified by TLC on silica gel with EtOAc–hexane (1:10) development to give methyl (+)-(2*S*,3*R*)-*trans*-3-(dimethoxymethyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (**28**, 630 mg, 42% yield): bp 80 °C (0.25 mmHg) (lit.[11] bp 114–115 °C (6 mmHg)), $[\alpha]^{25}$ +95.7° (*c* 0.28, $CHCl_3$); IR ν 1736 cm^{-1}; ^1H NMR δ 1.40–1.64 (m, 2 H), 2.02–2.36 (m, 1 H), 3.06–3.24 (m, 1 H), 3.32 (d, 6 H, *J* = 6 Hz), 4.24 (d, 1 H, *J* = 7.5 Hz), 5.94 (d of d, 1 H, *J* = 3 Hz), 6.26 (d of d. 1 H, *J* = 3 Hz).

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Registry No. 1, 699-97-8; **2**, 5062-98-6; **3**, 699-95-6; **4**, 5062-97-5; **5**, 57427-48-2; **6**, 65942-08-7; (+)-**10**, 95340-88-8; (±)-**10**, 95340-89-9; (+)-**11**, 95340-90-2; (±)-**11**, 95340-91-3; (+)-**12**, 95340-92-4; (±)-**12**, 95340-93-5; (+)-**13**, 95340-94-6; (±)-**13**, 95340-95-7; (+)-**14**, 95340-96-8; (±)-**14**, 95403-17-1; (+)-**15**, 95340-97-9; (±)-**15**, 95218-40-9; **16**, 95218-41-0; **17**, 15216-53-2; **18**, 95340-98-0; **19**, 95218-42-1; **20**, 95340-99-1; **21**, 95341-00-7; **22**, 95218-43-2; **23**, 95218-44-3; **24**, 95341-01-8; **25**, 95341-02-9; **26**, 95341-03-0; **27**, 57222-02-3; **28**, 95341-04-1; *cis*-*endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid anhydride, 129-64-6; *cis*-*exo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid anhydride, 2746-19-2; *cis*-*endo*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic acid anhydride, 24327-08-0; methyl (+)-(2*S*,3*R*)-*cis*-*exo*-3[(phenylselenyl)methyl]bicyclo[2.2.1]heptane-2-carboxylate, 95218-45-4; methyl (+)-(2*S*)-*exo*-bicyclo[2.2.1]heptane-3-one-2-carboxylate, 95341-05-2; methyl (+)-(2*R*)-*endo*-3-methylenebicyclo[2.2.1]heptane-2-carboxylate, 95341-06-3; methyl (+)-(2*S*,3*R*)-*cis*-3-[(tetrahydropyranyloxy)methyl]bicyclo[2.2.2]octane-2-carboxylate, 95218-46-5; methyl (+)-(2*R*,3*R*)-*trans*-3-[(tetrahydropyranyloxy)methyl]bicyclo[2.2.2]octane-2-carboxylate, 95341-07-4; alcohol dehydrogenase, 9031-72-5.

Exact Hückel Molecular Orbitals of the Finite, Square-Cut, FCC Crystal

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Abstract: The exact Hückel molecular orbitals of the finite, square-cut, FCC crystal are derived from the molecular orbitals of a "master", finite, cubic crystal by constructing the former from the latter by crossing out a series of atoms analogous to the starred atoms of an alternant hydrocarbon.

Although Bloch waves have been used for more than a generation to describe the tight-binding in infinite crystals,[1,2] little interest has focused on the wave functions for finite crystals. It was only in 1977 and 1979 that first Messmer,[3] in his "analytical

(1) See, for example: (a) Peierls, R. E. "Quantum Theory of Solids"; Oxford University Press; London, 1955. (b) Reitz, J. R. *Solid State Phys.* **1955**, *1*, 1.

(2) Slater, J. C.; Koster, G. F. *J. Chem. Phys.* **1954**, *94*, 1498. The matrix elements between plane waves in the infinite FCC crystal are given in Table III, terms with subscript 2.

(3) (a) Messmer, R. P. *Phys. Rev. B* **1977**, *15*, 1811. (b) Messmer, R. P. In "The Nature of the Surface Chemical Bond"; Rhodin, T. N., Ertl, G., Ed.; North Holland: Amsterdam, 1979: Chapter 2, pp 65–67. A much earlier reference is actually the following: Baldock, G. R. *Proc. Phys. Soc. London, Ser. A* **1953**, *66*, 2. Baldock gives the wave functions (1) for the simple cubic lattice and also for a BCC lattice bound by one (100) and two (110) type faces.

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