Enantio- and Regioselective Baeyer−Villiger Oxidations of 2- and 3-Substituted Cyclopentanones Using Engineered Bakers' Yeast

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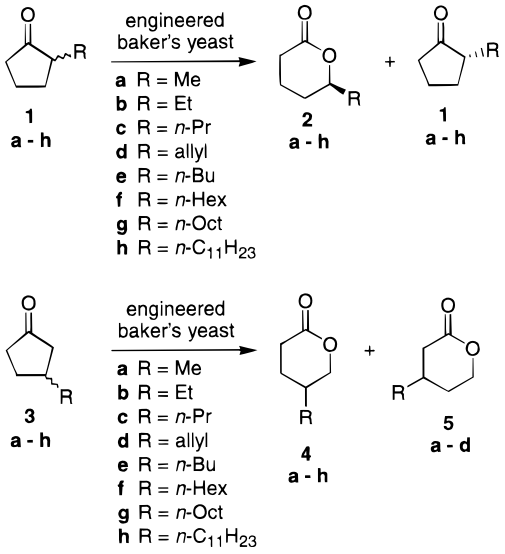
Received April 20, 1998

Introduction

We have reported the construction and evaluation of a new strain of bakers' yeast (*Saccharomyces cerevisiae*) that performs asymmetric Baeyer−Villiger oxidations on a variety of cyclohexanones.[1] This strain represents the first example of our engineered yeast strategy that allows nonspecialists to easily apply enzymes to asymmetric organic synthesis. The Baeyer−Villiger reaction is carried out by cyclohexanone monooxygenase, cloned from the bacterium *Acinetobacter* sp. NCIB 9871.[2] This enzyme was chosen because of its broad substrate tolerance and its high enantioselectivity (reviewed in ref 3). Our previous studies have focused on a complete series of alkyl-substituted cyclohexanones, and we found that the engineered yeast strain oxidized these compounds with high regio- and enantioselectivities.[1,4] Under the optimized conditions, no byproducts were formed and carbonyl reduction and lactone hydrolysis by yeast enzymes were not significant.

We also found that the same yeast oxidized cyclopentanone to δ-valerolactone in 67% yield.[1] Moreover, the work of Furstoss and co-workers suggested that cyclohexanone monooxygenase might also be useful for oxidations of substituted cyclopentanones.[5] Chiral substituted δ-valerolactones are valuable intermediates in organic synthesis[6−9] and Baeyer−Villiger oxidations of substituted cyclopentanones are an attractive route to these lactones. We therefore examined the oxidations of a series of 2- and 3-alkyl-substituted cyclopentanones using our engineered yeast strain. The results roughly parallel those previously observed for cyclohexanones: the enzyme selectively oxidizes (*S*)-2-alkyl-substituted cyclopentanones and displays useful regioselectivities in the oxidations of 3-alkyl-substituted cyclopentanones.

Scheme 1



Results and Discussion

2-Alkyl-substituted cyclopentanones (**1b**,**c**,**e**−**h**; Scheme 1) were prepared by alkylation and decarboxylation of methyl cyclopentanone-2-carboxylate. 2-Allylcyclopentanone **1d** was prepared by direct alkylation of cyclopentanone. An analogous series of 3-substituted cyclopentanones (**3b**−**h**; Scheme 1) was synthesized by Michael addition of the appropriate alkyl Grignard reagents to 2-cyclopenten-1-one in the presence of cuprous iodide.[10]

Yeast-mediated oxidations were carried out essentially as described previously,[1] and the results are summarized in Table 1. One equivalent of β-cyclodextrin (relative to the ketone) was included during the oxidations of **1g** and **1h** to overcome problems with substrate solubility.[11] In the case of 3-substituted cyclopentanones **3a**−**h**, this strategy was not useful: addition of either β- or γ-cyclodextrin to the reaction mixture resulted in substrate precipitation and the yields were inferior to those obtained from the reactions carried out in the absence of cyclodextrins. The reactions were sampled periodically and analyzed by chiral-phase GC. We were able to achieve baseline resolution of all enantiomers except lactones **4e**−**h**. Absolute configurations of **1c**−**h** and **2c**−**h** were deduced by comparing the signs of the optical rotations with literature values.[5,12−14] Optical rotation data for **1f** and **2f** were unavailable, and we have

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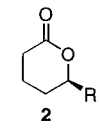
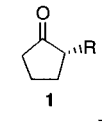
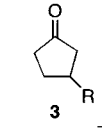
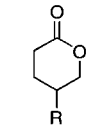
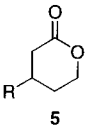
S0022-3263(98)00737-3 CCC: $15.00
Published on Web 09/09/1998

Table 1. Oxidations of Substituted Cyclopentanones by Engineered Bakers' Yeast

		a, R = Me	**b**, R = Et	**c**, R = *n*-Pr	**d**, R = allyl	**e**, R = *n*-Bu	**f**, R = *n*-Hex	**g**, R = *n*-Oct	**h**, R = *n*-$C_{11}H_{23}$
 **2**	Yield[a]	36%[b]	44%[b]	51%	76%	18%	32%	25%	39%
	%ee[c]	32%	39%	67%	32%	≥ 98%	≥ 98%	≥ 98%	≥ 98 %
	$[\alpha]_D$[d]	N.D.[e]	N.D.	-26°, *c* 0.97	-8.1°, *c* 1.1	-48°, *c* 0.83	-44°, *c* 0.98	-35.0°, *c* 1.38	-12°, *c* 0.55
 **1**	Yield	34%[b]	37%[b]	21%	10%	32%	42%	14%	37%
	%ee	44%	46%	72%	51%	≥ 98%	≥ 98%	≥ 98%	≥ 98%
	$[\alpha]_D$	N.D.	N.D.	-110°, c 0.68	-73°, c 0.42	-160°, c 0.78	-110°, c 0.70	-110°, c 0.46	-70.5°, c 2.19
	E[f]	3.6	3.7	30	2.3	≥ 200	≥ 200	≥ 200	≥ 200
	Ref.	12	13	12	14	12		12	5
 **3**	Yield	0%	10%[b]	27%	55%[b]	44%	54%	44%	54%
	%ee	--	19%	13%	N.D.	25%	29%	8%	16%
	$[\alpha]_D$	--	N.D.	+18°, *c* 2.5	N.D.	+16°, *c* 1.4	+18°, *c* 1.5	N.D.	N.D.
 **4**	%ee	9%	33%	33%	23%	38%	60%	16%	N.D.
 **5**	%ee	36%	19%	60%	N.D.	--	--	--	--
	Conversion	100%	86%	53%	43%	44%	32%	31%	23%
	Overall Yield	95%	80%[b]	44%	42%[b]	34%	20%	19%	20%
	4 : **5**[h]	13 : 87	80 : 20	83 : 17	44 : 56	> 99 : < 1	> 99 : < 1	> 99 : < 1	> 99 : < 1

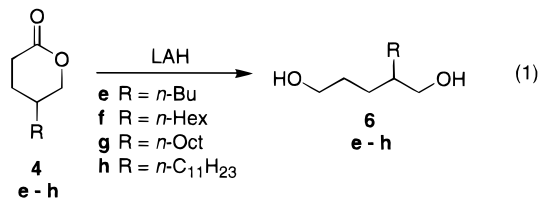
[a] Yields refer to chromatographically purified samples unless otherwise indicated. [b] Yields determined by gas chromatography using an internal standard. [c] Values of enantiomeric excess were determined by chiral-phase GC analysis. [d] Optical rotations were measured from $CHCl_3$ solutions at ambient temperature. [e] Not determined. [f] Enantioselectivity values were calculated from plots of ee(substrate) *versus* fractional conversion. [g] This isomer was not detected by capillary GC analysis. [h] Regioisomeric composition of reactions that had proceeded to the indicated fractional conversion.

therefore assigned these absolute configurations by analogy with our other results. Enantioselectivity values for the oxidations of **1a**−**h** were determined by nonlinear least-squares fitting as described previously.[4,15]

Cyclohexanone monooxygenase exhibits virtually complete enantioselectivity for the (*S*)-enantiomer of 2-alkyl-substituted cyclohexanones, provided that the substituent is larger than methyl.[4a] This enantioselectivity allows for efficient kinetic resolutions in these systems. The same general trend was observed for 2-alkyl-substituted cyclopentanones, although high enantioselectivities required at least a four-carbon substituent (Table 1). In the cases of **1e**−**h**, optically pure ketone and lactone could be isolated from a single biotransformation starting from the racemic ketone.

The yeast-mediated oxidations of racemic **3a**−**d** produced both possible lactone regioisomers (**4** and **5**; Table 1). Similar behavior had been previously observed in the enzymatic oxidations of 3-methyl- and 3-ethylcyclohexanone, although the optical purities of the lactone regioisomers were higher in these cases.[3] Unfortunately, the regioisomeric δ-valerolactones could not be separated chromatographically; however, the structures of the lactone regioisomers in the product mixtures were conclusively established from 2-D NMR spectra. Optical purities were determined by chiral-phase GC analysis using conditions that allowed baseline resolution of all components.

In contrast to the above results, 3-alkyl-substituted cyclopentanones **3e**−**f** were oxidized to single regioisomers according to GC and 2-D NMR analyses of the crude reaction mixtures. Since it was not possible to resolve the enantiomeric δ-valerolactones by chiral-phase GC, these compounds were reduced by $LiAlH_4$ to diols that could be resolved (eq 1). This reduction also confirmed



(1)

the regiochemistry of lactones **4e**−**h**.[16] Because of the low enantioselectivities of these reactions, we did not attempt to assign absolute configurations to the isolated ketones and lactones. The major utility of these reactions lies in their ability to produce exclusively 5-alkyltetrahy-

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(16) Reduction of the alternate regioisomer would have produced a *meso* diol. ^{13}C NMR data were not consistent with a symmetrical molecule.

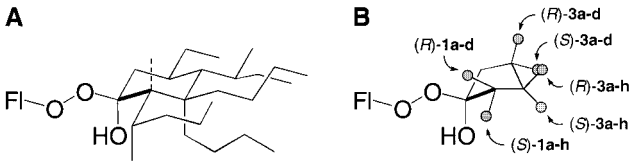

Figure 1. Active site models for cyclohexanone monooxygenase. A. Diamond lattice model of the tetrahedral intermediate derived from studies of substituted cyclohexanones.[17] The migrating carbon−carbon bond is indicated by a heavy line. The locations of substituents tolerated by the enzyme are illustrated by solid lines. The dotted line indicates that an axial methyl group is partially tolerated in this position. B. Analogous conformation for the tetrahedral intermediates involved in oxidations of 2- and 3-substituted cyclopentanones. Allowed positions of substituents are depicted in cartoon form, and the lengths of the side chains tolerated at these positions are indicated by the compound numbers of the corresponding ketones. Note the good overall similarity between the size of allowed cyclopentanone substituents and the dimensions of the active site as determined by the diamond lattice model.

dropyran-2-ones in a transformation that cannot be duplicated by organic peracids. Moreover, preliminary experiments indicate that yields can be significantly improved by the use of lower ketone concentrations during the biotransformations.

The behavior of 2- and 3-substituted cyclopentanones can be rationalized by considering the conformational behavior of the substrates and the active site structure of the enzyme. The principal differences between the behavior of cyclopentanones and cyclohexanones can be ascribed to the low-energy barriers between alternate cyclopentane conformations and the accessibility of half-chair structures in this ring system. The results from the present study have been summarized in Figure 1, which also depicts our diamond lattice model of the enzyme active site based on studies of cyclohexanones.[17] Both enantiomers of 2-substituted cyclopentanones were oxidized to the same regioisomer, which meant that the substituted carbon was always located in the same position. For the (*S*)-enantiomer, the substituent can occupy a pseudoequatorial position; however, the substituent in the (*R*)-enantiomer must be located in a pseudoaxial position. For cyclohexanones, this conformational difference provides a large fraction of the observed selectivity for the (*S*)-ketones.[4b] By contrast, the energy differences between substituents in pseudoaxial and pseudoequatorial positions of cyclopentanes in the twist boat conformation are minimal,[18] so that this reinforcement is largely absent for all of the 2-substituted cyclopentanones (**1a**−**h**). The high enantioselectivities observed for **1e**−**h** must therefore result from additional favorable interactions between the long side chain and the active site of the enzyme. The relatively small enantioselectivities observed for 3-subsituted cyclopentanones are also likely to be due to the near-equivalence of pseudoaxial and pseudoequatorial conformations. As in the case of cyclohexanones, the regioselectivities observed for compounds with long side chains probably reflects specific contacts between the protein and these substrates.

Compared to analogous cyclohexanones, cyclohexanone monooxygenase displays relatively less regio- and enantioselectivities for substituted cyclopentanones. However, for certain specific cases, our designer yeast methodology makes important chiral building blocks easily available in high optical (**1e**−**h**; **2e**−**h**) and regiochemical purities (**4e**−**h**). For example, lactone **2h** is a pheromone isolated from the oriental hornet *Vespa orientalis*,[19] and our methodology makes it easily available in optically pure form. To show that this methodology can accommodate larger quantities of substrates, the oxidation of ketone **1f** was carried out on a 0.45 g scale and the (*R*)-ketone and (*S*)-lactone were isolated in 78% and 88% yields, respectively.

Experimental Section

General. Packed column gas chromatography was performed using a 5% OV-101 on 100/120 Supelcoport (1/8 in. × 1 m) column with helium as carrier gas. Capillary gas chromatography separations utilized a 0.32 mm × 30 m × 0.25 μm column using helium as the carrier gas. The injector and detector temperatures were maintained at 225 °C. Thin-layer chromatography was performed on precoated silica gel 60 plates. Reaction products were purified by flash chromatography using 200−425 mesh silica gel.[20] Tetrahydrofuran and diethyl ether were distilled from K−Na alloy in the presence of benzophenone. Potassium carbonate was dried at 80 °C and cooled to room temperature in a desiccator prior to use. Acetone was dried over $CaSO_4$ and distilled from $KMnO_4$. Methylene chloride was dried over anhydrous K_2CO_3, distilled and stored over 3 Å molecular sieves. All solvents were purified by fractional distillation. Other reagents were obtained from commercial suppliers and used as received.

Preparation of Yeast Cells. A 200 mL portion of YPD (1% Bacto-Yeast Extract, 2% Bacto-Peptone, 2% glucose) in a 500 mL baffled conical flask was inoculated with a single colony of yeast. The flask was agitated on a rotatory shaker at 30 °C. When the OD_{600} of the culture reached 4.0, the cells were harvested by centrifuging at 3000*g* for 10 min at 20 °C. The yeast pellet was transferred to a second 500 mL conical flask containing 200 mL of YP-Gal (1% Bacto-Yeast Extract, 2% Bacto-Peptone, 2% galactose). Cyclopentanone (20 μL) was added, and the reaction was allowed to proceed for 3−4 h until the OD_{600} reached 6−8.[21] The yeast was harvested by centrifugation as above, and the pellet was washed 3 times with TE (10 mM Tris-Cl, pH 7.5, 1 mM EDTA). After this, the yeast cells were resuspended in 10 mM Tris-Cl, pH 7.5, 1 mM EDTA, 15% glycerol at a concentration of 0.2 g/mL. This was divided into 1 mL aliquots and frozen at −80 °C prior to use in biotransformations. These frozen stocks did not show significant loss of activity for at least 1 month.

General Procedure for Yeast Mediated Baeyer−Villiger Oxidations. The ketone substrate (100 μL) was added to YP-Gal (100 mL) in a 250 mL baffled conical flask. When necessary, 1 equiv of β- or γ-cyclodextrin (relative to the ketone) was included. The mixture was then shaken at 30 °C at 250 rpm for 5−10 min to obtain a uniform dispersion. A 1 mL portion of yeast cells was added to the reaction flask; then the culture was

(17) While other models for the active site of cyclohexanone monooxygenase have been constructed independently, the close structural relationship between the cyclopentanones and the cyclohexanones used to construct this model make it especially convenient for the present purpose. Other cyclohexanone monooxygenase active site models: Taschner, M. J.; Peddada, L.; Cyr, P.; Chen, Q. Z.; Black, D. J. *NATO ASI Ser., Ser. C* **1992**, *381*, 347−360; Alphand, V.; Furstoss, R. *J. Org. Chem.* **1992**, *57*, 1306−1309; Kelly, D. R. *Tetrahedron: Asymmetry* **1996**, *7*, 1149−1152; Ottolina, G.; Pasta, P.; Carrea, G.; Colonna, S.; Dallavalle, S.; Holland, H. L. *Tetrahedron: Asymmetry* **1995**, *6*, 1375−1386; Ottolina, G.; Carrea, G.; Colonna, S.; Rückemann, A. *Tetrahedron: Asymmetry* **1996**, *7*, 1123−1136.

(18) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry. Part B: Reactions and Synthesis*; 2nd ed.; Plenum: New York, 1983.

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(20) Still, W. C.; Kahn, M.; Mitra., A. *J. Org. Chem.* **1978**, *15*, 2923−2925.

(21) The inclusion of cyclopentanone during this step was empirically found to increase the efficiency of the yeast cells during the subsequent Baeyer−Villiger oxidations.

was shaken at 30 °C at 250 rpm and the reaction was monitored by GC. Once the conversion reached approximately 50% (or when the ratio of products remained constant), the yeast cells were removed by centrifugation. The yeast cell pellet was suspended in 50 mL of distilled water; then this was extracted with ethyl acetate (2 × 100 mL). The aqueous growth medium was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed once with brine, dried over anhydrous Na_2SO_4 or $MgSO_4$, and concentrated by rotary evaporation. Pure products were isolated by flash chromatography. For reaction mixtures derived from **1a**−**h**, 3:1 hexane:diethyl ether followed by 1:1 hexane:diethyl ether was used for chromatographic purifications. For reaction mixtures derived from 3-substituted cyclopentanones, petroleum ether:acetone (5:1) was used for **3a** and **3b** and a 10:1 ratio of these solvents was used for **3c**−**h**. After the ketones had been completely eluted, chromatography was continued with petroleum ether:acetone (3:1) until the lactones had been eluted.

Larger-Scale Oxidation of 2-*n*-Hexylcyclopentanone 1f. γ-Cyclodextrin (2.3 mmol, 3.0 g) and 2-*n*-hexylcyclopentanone **1f** (2.7 mmol, 0.45 g) were added to a 2 L Erlenmeyer flask containing 1 L of YP-Gal. The resulting mixture was shaken at 200 rpm for 24 h at 30 °C to obtain a uniform suspension; then 1 g of frozen yeast cells was added. The culture was shaken at 200 rpm for 60 h at 30 °C; then the yeast cells were removed by centrifugation. The supernatant was extracted with petroleum ether (4 × 250 mL). The cell pellet was suspended in 100 mL of water; then it was extracted with petroleum ether (4 × 75 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. Chromatographic purification using 10:1 petroleum ether−acetone afforded ketone **1f** (0.18 g, 78% yield) and lactone **2f** (0.22 g, 88% yield, 96% ee).

Spectral Data for New Compounds. 6-*n*-Propyltetrahydropyran-2-one 2c. IR (neat) ν: 1732 cm^{-1}. ^1H NMR: δ 4.27 (1H, m), 2.34 (1H, m), 2.40 (1H, m), 1.92−1.74 (3H, m), 1.66 (1H, m), 1.50 (3H, m), 1.39 (1H, m), 0.90 (3H, t, J = 7.2 Hz) ppm. ^{13}C NMR δ 171.9, 80.3, 37.8, 29.4, 27.7, 18.4, 18.1, 13.8 ppm. MS: *m/e* 142 (M^+, 1.4), 99 (100), 71 (50), 70 (35), 55 (26).

6-Allyltetrahydropyran-2-one 2d. IR (neat) ν: 1734 cm^{-1}. ^1H NMR: δ 5.78 (1H, m), 5.14 (2H, m), 4.32 (1H, m), 2.55 (1H, m), 2.50−2.40 (2H, m), 2.36 (1H, m), 1.89 (2H, m), 1.80 (1H, m), 1.51 (1H, m) ppm. ^{13}C NMR δ 171.6, 132.6, 118.5, 79.7, 40.0, 29.4, 27.1, 18.4 ppm. MS: *m/e* 99 (M^+ − 45, 100), 71 (66), 55 (29).

6-*n*-Butyltetrahydropyran-2-one 2e. IR (neat) ν: 1731 cm^{-1}. ^1H NMR: δ 4.26 (1H, m), 2.55 (1H, m), 2.42 (1H, m), 1.94−1.76 (3H, m), 1.67 (1H, m), 1.60−1.40 (3H, m), 1.32 (3H, m), 0.88 (3H, t, J = 7.2 Hz) ppm. ^{13}C: NMR δ 172.0, 80.6, 35.5, 29.4, 27.8, 27.0, 22.5, 18.5, 13.9 ppm. MS: *m/e* 156 (M^+, 1), 99 (100), 71 (46), 70 (27), 55 (27).

6-*n*-Octyltetrahydropyran-2-one 2g. IR (neat) ν: 1743 cm^{-1}. ^1H NMR δ 4.26 (1H, m), 2.55 (1H, m), 2.42 (1H, m), 1.92−1.75 (3H, m), 1.68 (1H, m), 1.50 (3H, m), 1.26 (11H, m), 0.86 (3H, t, J = 7.2 Hz) ppm. ^{13}C NMR: δ 172.0, 80.6, 35.8, 31.8, 29.5, 29.44, 29.41, 29.2, 27.8, 24.9, 22.6, 18.5, 14.1 ppm. MS: *m/e* 194 (M^+ − 18, 1), 99 (100), 71 (36), 70 (29), 55 (31).

5- and 4-Methyltetrahydropyran-2-ones 4a and 5a (13:87 ratio). Spectral data were obtained from the inseparable mixture. Many spectral signals overlapped and only those that were distinct are reported. IR (neat) ν: 1745, 1731 cm^{-1}. **4a.** ^1H NMR: δ 4.32 (1H, dd, J = 4.6 Hz, J = 2.2 Hz), 3.91 (1H, t, J = 10.1 Hz), 3.86 (1H, t, J = 6.7 Hz), 1.01 (3H, d, J = 6.7 Hz) ppm. ^{13}C NMR: δ 171.2, 74.8, 39.1, 29.0, 27.4, 16.4 ppm. MS: *m/e* 114 (M^+, 15), 84 (25), 70 (31), 56 (100), 55 (45). **5a.** ^1H NMR: δ 4.43 (1H, m), 4.27 (1H, m), 1.07 (3H, d, J = 6.2 Hz) ppm. ^{13}C NMR: δ 171.2, 68.5, 38.1, 30.5, 26.4, 21.3 ppm. MS: *m/e* 114 (M^+, 31), 70 (24), 56 (56), 55 (100).

5- and 4-Ethyltetrahydropyran-2-ones 4b and 5b (80:20 ratio). Spectral data were obtained from the inseparable mixture. Many spectral signals overlapped, and only those that were distinct are reported. IR (neat) ν: 1743 cm^{-1}. MS: *m/e* 128 (M^+, 4), 99 (100),71 (71), 70 (31), 56 (30), 55 (33). **4b.** ^1H NMR: δ 4.33 (1H, ddd, J = 11.2 Hz, J = 8.8 Hz, J = 2.0 Hz), 3.93 (1H, dd, J = 11.1 Hz, J = 9.7 Hz), 0.87 (3H, t, J = 7.3 Hz) ppm. ^{13}C NMR: δ 171.5, 73.4, 34.4, 25.1, 24.5, 22.4, 11.3 ppm. **5b.** ^1H NMR: δ 4.39 (1H, m), 4.22 (1H, td, J = 10.4 Hz, J = 3.6 Hz), 0.91 (3H, t, J = 7.3 Hz) ppm. ^{13}C NMR: δ 171.5, 68.5, 36.3, 33.1, 28.9, 28.5, 10.9 ppm.

5- and 4-Propyltetrahydropyran-2-ones 4c and 5c (83:17 ratio). Spectral data were obtained from the inseparable mixture. Many spectral signals overlapped, and only those that were distinct are reported. IR (neat) ν: 1743 cm^{-1}. **4c.** ^1H NMR: δ 4.30(1 H, m), 3.91 (1H, m) ppm. ^{13}C NMR: δ 171.62, 73.6, 33.6, 32.5, 29.0, 25.4, 19.9, 14.0 ppm. MS: *m/e* 142 (M^+, 5), 84 (100), 70 (33), 69 (32), 56 (51), 55 (74). **5c.** ^1H NMR: δ 4.37 (1H, m), 4.21 (1H, m) ppm. ^{13}C NMR: δ 171.57, 68.5, 38.3, 36.5, 31.1, 19.5, 18.7, 13.9 ppm. MS: *m/e* 99 (M^+ − 43, 82), 84 (34), 70 (57), 69 (68), 56 (100), 55 (95).

5- and 4-Allyltetrahydropyran-2-ones 4d and 5d (44:56 ratio). Spectral data were obtained from the inseparable mixture. IR (neat) ν: 1726 cm^{-1}. **5d.** ^1H NMR: δ 4.39 (1H, m), 4.24 (1H, m), 2.64 (1H, m), 2.50 (1H, dd, J = 9.6 Hz, J = 7.0 Hz) ppm (all other ^1H NMR signals overlap). ^{13}C NMR: δ 171.2, 134.5, 117.8, 68.4, 40.2, 36.1, 31.2, 28.4 ppm. **4d.** ^1H NMR δ 4.32 (1H, m), 3.96 (1H, dd, J = 11.3 Hz, J = 9.1 Hz), 2.68 (1H, dd, J = 5.5 Hz, J = 1.4 Hz), 2.59 (1H, dd, J = 6.8 Hz, J = 4.4 Hz) ppm (all other ^1H NMR signals overlap). ^{13}C NMR: δ 171.4, 134.6, 117.6, 73.1, 35.9, 32.4, 29.0, 25.1 ppm.

5-*n*-Butyltetrahydropyran-2-one 4e. IR (neat) ν: 1740 cm^{-1}. ^1H NMR: δ 4.30 (1H, ddd, J = 11.1 Hz, J = 4.6 Hz, J = 2.1 Hz), 3.93 (1H, dd, J = 10.9 Hz, J = 9.7 Hz), 2.59 (1H, m), 2.46 (1H, m), 1.98 (1H, m), 1.87 (1H, m), 1.50 (1H, m), 1.28 (6H,m), 0.87 (3H, t, J = 6.8 Hz) ppm. ^{13}C NMR: δ 171.6, 73.7, 32.8, 31.2, 29.0, 28.9, 25.5, 22.7, 13.9 ppm. MS: *m/e* 156 (M^+, 2), 98 (100), 84 (33), 70 (65), 69 (56), 56 (72), 55 (79).

5-*n*-Hexyltetrahydropyran-2-one 4f. IR (neat) ν: 1743 cm^{-1}. ^1H NMR: δ 4.31 (1H, ddd, J = 11.1 Hz, J = 4.4 Hz, J = 1.9 Hz), 3.92 (1H, dd, J = 11.1 Hz, J = 9.7 Hz), 2.59 (1H, m), 2.47 (1H, m), 1.98 (1H, m), 1.86 (1H,m), 1.50 (1H, m), 1.20−1.36 (10H, m), 0.86 (3H, t, J = 7.2 Hz) ppm. ^{13}C NMR: δ 171.5, 73.7, 32.8, 31.6, 31.5, 29.3, 29.1, 26.7, 25.5, 22.6, 14.0 ppm. MS: *m/e* 154 (M^+ − 30, 1), 128 (23), 98 (100), 84 (30), 70 (50), 69 (50), 56 (38), 55 (71).

5-*n*-Octyltetrahydropyran-2-one 4g. IR (neat) ν: 1742 cm^{-1}. ^1H NMR: δ 4.32 (1H, ddd, J = 11.1 Hz, J = 4.6 Hz, J = 2.0 Hz), 3.93 (1H, dd, J = 11.1 Hz, J = 9.7 Hz), 2.60 (1H, m), 2.48 (1H, m), 1.99 (1H, m), 1.87 (1H, m), 1.49 (1H, m), 1.25 (14H, m) 0.86 (3H, t, J = 6.7 Hz) ppm. ^{13}C NMR: δ 171.6, 73.7, 32.8, 31.8, 31.5, 29.6, 29.4, 29.2, 26.8, 25.5, 22.7, 22.4, 14.1 ppm. MS: *m/e* 212 (M^+, 1), 150 (33), 128 (22), 98 (100), 97 (48), 83 (47), 70 (43), 69 (48), 55 (72).

5-*n*-Undecyltetrahydropyran-2-one 4h. IR (neat) ν: 1742 cm^{-1}. ^1H NMR δ 4.32 (1H, ddd, J = 11.1 Hz, J = 4.6 Hz, J = 1.9 Hz), 3.93 (1H, dd, J = 11.1 Hz, J = 9.7 Hz), 2.60 (1H, m), 2.48 (1H, m), 1.98 (1H, m), 1.87 (1H, m), 1.48 (1H, m), 1.27 (20H, m), 0.86 (3H, t, J = 6.7 Hz) ppm. ^{13}C NMR: δ 171.7, 73.7, 40.2, 36.9, 32.8, 31.9, 31.7, 31.5, 31.0, 29.9, 29.7, 29.6, 29.4, 26.7, 22.7, 14.1 ppm. MS: *m/e* 254 (M^+, 3), 192 (100), 141 (38), 111 (57), 98 (89), 83 (73), 69 (66), 55 (95).

$LiAlH_4$ Reduction of Lactones 4e−h. A 5 mL round-bottomed flask containing $LiAlH_4$ (20 mg) was flushed with nitrogen. THF (1 mL) was added via syringe, and the suspension was stirred at 0 °C for 10 min. The lactone (5 mg) dissolved in $CDCl_3$ (100 μL) was added slowly to the reaction flask, and the mixture was stirred for another 30 min at this temperature. The reaction was quenched by injecting 1 mL of saturated aqueous tartaric acid; then the product was extracted with 15 mL of $CHCl_3$. The organic extract was dried over anhydrous Na_2SO_4, and the solution was concentrated on a rotatory evaporator. Chiral-phase GC analysis of the product afforded the enantiomeric composition of the original lactone sample.

Acknowledgment. This work was supported financially by the National Science Foundation (CHE-9513349; J.D.S.) and by the Natural Sciences and Engineering Research Council and the University of New Brunswick (M.M.K.). We would like to thank Cerestar, Inc., for supplying the cyclodextrins used in this study, Kieth W. Reed and Elise R. Manning for preliminary studies in this area and Marko D. Mihovilovic for helpful discussions.

JO980737V