Application of Bakers' Yeast Mediated Reductions of Bicyclo[4.2.0]oct-2-en-7-ones to the Enantioselective Synthesis of Prostacyclin Analogues[1]

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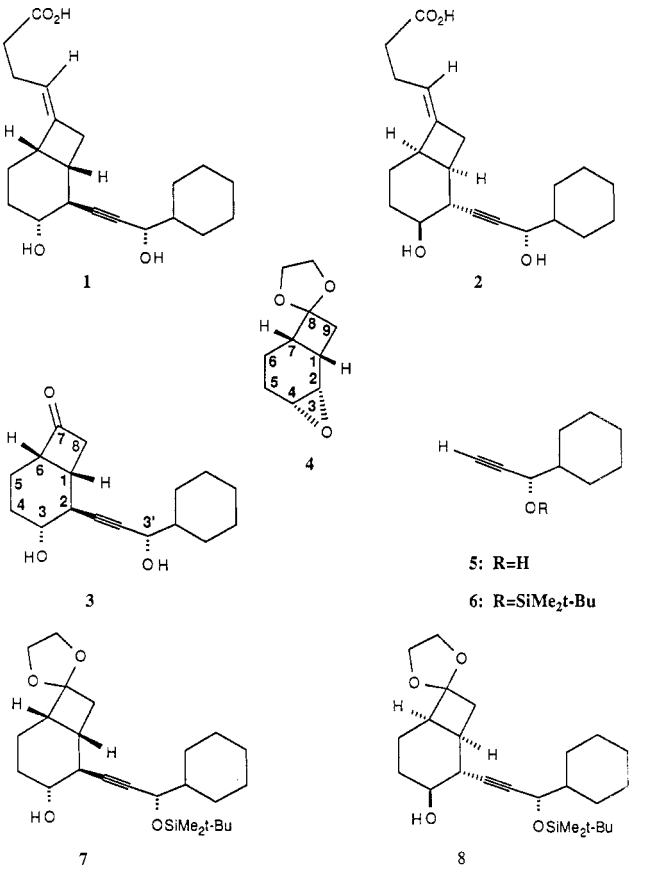
Reduction of 8,8-dichlorobicyclo[4.2.0]oct-2-en-7-one (**14**) with bakers' yeast gave (1*R*,6*S*,7*S*)-8,8-dichlorobicyclo[4.2.0]oct-2-en-7-ol [(*S*)-**15**] and (1*S*,6*R*)-8,8-dichlorobicyclo[4.2.0]oct-2-en-7-one [(*R*)-**14**] in high optical purities and 27% and 14% yields, respectively. Both (*S*)-**15** and the (1*S*,6*R*,7*R*)-8,8-dichlorobicyclo[4.2.0]oct-2-en-7-ol [(*R*)-**15**] formed by reduction of (*R*)-**14** with $NaBH_4$ were crystalline and readily gave materials of ≥99% ee on single recrystallizations. Yeast-mediated reductions in the bicyclo[4.2.0]oct-2-en-7-one system gave exclusively endo-alcohol products, and both the direction of enantioselectivity and the reaction rate were dependent on ketone α-substitution. The reduction of 8,8-dichloro ketone **14** was markedly faster than that of either 8-endo-monochloride **16** or of 8-unsubstituted **12**, and the chloro ketones **14** and **16** both gave alcohol products of 6*S* stereochemistry while **12** gave the 6*R* alcohol (*R*)-**13**. The relative stereochemistry of the products was established by using NOE NMR experiments and single-crystal X-ray analysis. Absolute stereochemistry was established by the conversion of dichloro alcohol (*S*)-**15** into keto diol **3**, a key intermediate in the synthesis of the platelet antiaggregatory prostacyclin analogue **1** (RS-93427-007).

Introduction

The application of biocatalytic reactions to organic synthesis has frequently provided highly practical and efficient means of preparing chiral molecules. Several excellent and recent reviews have summarized the uses of isolated enzymes and microbes in organic synthesis.[2] The numerous accounts of chemoselective and enantioselective transformations obtained through the use of the oxidoreductase, hydrolase, and ligase activities of enzymes coupled with the ease of procedural methodology have influenced many organic chemists to explore opportunities for employing these unconventional "reagents". The present paper relates to just such an application of a reduction with bakers' yeast to the enantioselective preparation of a novel pharmaceutical agent.

The diastereomeric prostacyclin analogues **1** and **2** have both been reported to be potent and orally active inhibitors of the aggregation of human platelets[3] (Chart I). Moreover, compound **1** (RS-93427-007) has shown biological activity that indicates potential utility in the therapy of atherosclerosis.[4] The need for substantial quantities of **1** for the conduct of toxicological and clinical studies required the development of an efficient synthesis of the keto diol **3**, which had been a key intermediate in a previously reported synthesis of **1**.[5] Keto diol **3** had been prepared via the regioselective boron trifluoride etherate assisted opening of the racemic bicyclo[4.2.0]octane epoxide **4** with the lithium acetylide corresponding to the resolved and suitably protected propargylic *S*-carbinol **5**. This reaction produced the two diastereomeric products **7** and **8**, which were then separated by a procedure involving treatment of the mixture with dicobalt octacarbonyl. Chromatographic separation of the resulting acetylene–dicobalt hexacarbonyl complexes followed by oxidative decomposition of the complexes afforded optically pure **7** and **8**, and deprotection of **7** then gave **3**. This sequence was not suited to large scale operation since purification of the acetylene–cobalt complexes by flash chromatography was limited to batches of ca. 50 g. In addition, the loss of the ca. 50% of resolved propargylic alcohol **5** that accompanied formation of the unwanted diastereomer **8** was clearly undesirable.

Chart I[a]



[a] Racemic epoxide **4** is represented by the structure of the single 7*S*-enantiomer for clarity.

(1) Contribution No. 739 from the Institute of Organic Chemistry.

(2) (a) Whitesides, G. M.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 617. (b) Sih, C. J.; Chen, C.-S. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 570. (c) Simon, H.; Bader, J.; Guenther, H.; Neuman, S.; Thanos, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 539. (d) Jones, J. B. *Tetrahedron* **1986**, *42*, 3351.

(3) Kluge, A. F.; Wu, H. Y.; Kertesz, D. J.; O-Yang, C. *Abstracts of Papers*, 6th International Conference on Prostaglandins and Related Compounds, Fondazione Giovanni Lorenzini; Milan, Italy, 1986; p 273.

(4) Willis, A. L.; Smith, D. L.; O-Yang, C.; Vigo, C.; Strosberg, A.; Wu, H.; Kertesz, D. J.; Kluge, A. F.; Roszkowski, A. P. *Abstracts of Papers*, 6th International Conference on Prostaglandins and Related Compounds, Fondazione Giovanni Lorenzini; Milan, Italy, 1986; p 98.

(5) Kluge, A. F.; Kertesz, D. J.; O-Yang, C.; Wu, H. Y. *J. Org. Chem.* **1987**, *52*, 2860.

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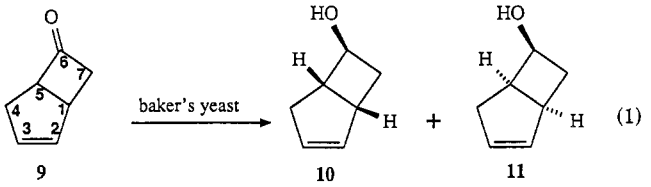
Since only the desired ketal diastereomer **7** would be produced by reaction of the single 7*S* enantiomer of epoxide **4** with the reagent derived from **5**, we began to search for an efficient enantioselective synthesis of **4**. A resolution of the precursor bicyclo[4.2.0]oct-2-en-7-one **12** employing the formation of diastereomeric oxazolidines with *l*-ephedrine had been reported,[6] but this method failed in our hands. A series of similar attempts at resolution of **12** through formation of diastereomeric ketal-type derivatives with optically active difunctional compounds (e.g. diethyl D-tartrate,[7] *l*-mandelic acid, *l*-malic acid, and D-mannitol bisacetonide) were also unsuccessful, as was an attempt at forming separable (+)-α-methylbenzylamine salts of the ketone bisulfite addition products.[8] A resolution of **12** utilizing bakers' yeast was then attempted, based on a report that a yeast reduction of bicyclo[3.2.0]hept-2-en-6-one (**9**) had given the diastereomeric 5*S*-exo and 5*R*-endo alcohols **10** and **11**, respectively, as chromatographically separable products of high optical purity (eq 1).[9] We expected that similar substrate no-



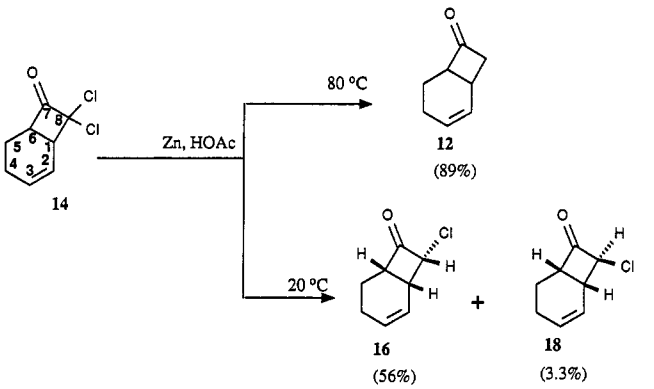
(1)

nenantioselective yeast reductions would occur in our bicyclooctenone system. A highly optically enriched 6*S* bicyclooctenol product analogous to **10** would have the required absolute stereochemistry for the projected enantioselective synthesis of **3**.

Results and Discussion

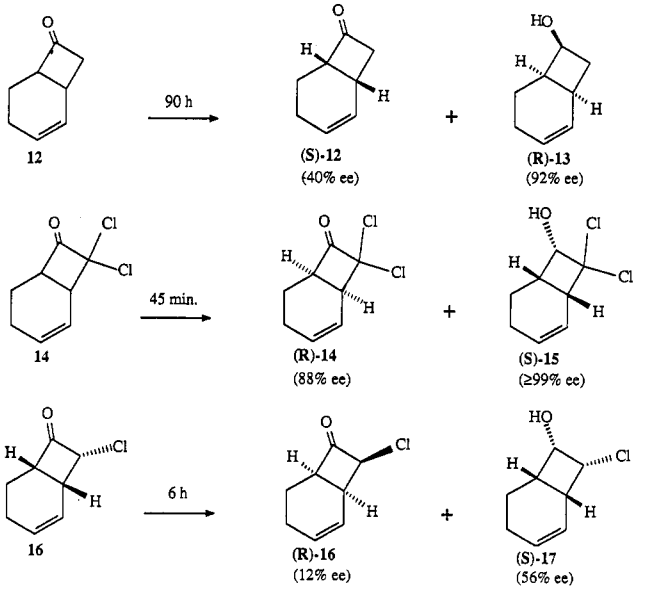
The bicyclo[4.2.0]oct-2-en-7-one substrates used in our yeast reduction study were the known unsubstituted ketone **12** and 8,8-dichloro ketone **14**,[10] and the 8-endo-monochloro ketone **16**.[11] Ketone **12** was obtained by the reduction of **14** with zinc and acetic acid at 80 °C (5 h, 89% yield), and monochloro ketone **16** was prepared by a reduction of **14** with the same reagents under less vigorous conditions (15 min at 20 °C, 56% yield) (Scheme I). Preparation of **16** was accompanied by the isolation of 3.3% of the 8-exo-chloro ketone **18**,[11] the structures being assigned on the basis of the nuclear Overhauser enhancement (NOE) effects observed in proton NMR spectra. Conditions used for the yeast reductions represented an average of several literature precedents. A typical yeast reaction consisted of a stirred mixture of 1

Scheme I. Zinc Reductions[a]



[a] Racemic ketones **16** and **18** are represented by structures of the single 6*S*-enantiomers for clarity.[11a]

Scheme II. Bakers' Yeast Reductions[a]



[a] Racemic ketone **16** is represented by the structure of the single 6*S*-enantiomer for clarity.[11a]

part of ketone with 7–15 parts of common bakers' yeast, 1 part of a "nutritional" yeast extract,[12] and 1 part of sucrose in 160 parts of 5% ethanol in water at 33 °C, with progress being monitored by TLC.

Reductions of Bicyclo[4.2.0]octenones with Bakers' Yeast. To our surprise, the reactions of the bicyclo[4.2.0]octenones **12**, **14**, and **16** with bakers' yeast were found to be completely diastereoselective for reduction from the ketone exo face, in addition to being highly enantioselective. The products isolated from each reaction consisted exclusively of a single endo-alcohol of high optical purity and unreacted ketone enriched in the other enantiomer, rather than being the pairs of diastereomeric alcohols anticipated from the bicyclo[3.2.0]heptenone precedent (Scheme II). A predictable and ultimately useful reversal of product enantioselectivity determined by the ketone α-substitution pattern was also noted, with the unsubstituted ketone **12** giving a 6*R* alcohol product whereas both of the 8-chloro ketones **14** and **16** afforded the more desirable 6*S* alcohols as products. In addition, the reduction of dichloroketone **14** was characterized by re-

(6) Bundy, L. L.; Nelson, N. A. U.S. Patent 4 130 721, 1978. See also: Kelly, R.; Van Rheenen, V. *Tetrahedron Lett.* **1973**, *19*, 1709.

(7) For a successful resolution using this reagent, see: Delmuth, M.; Chandrasekhar, S.; Schaffner, K. *J. Am. Chem. Soc.* **1984**, *106*, 1092.

(8) This method was reported to be successful for the resolution of bicyclo[3.2.0]hept-2-en-3-one (**9**): Wallis, C. J. Eur. Pat. Appl. EP 74 856, 1983. See also: Collington, E. W.; Wallis, C. J.; Waterhouse, I. *Tetrahedron Lett.* **1983**, *24*, 3125.

(9) Newton, R. F.; Paton, J.; Reynolds, D. P.; Young, S.; Roberts, S. M. *J. Chem. Soc., Chem. Comm.* **1979**, 908. Similar results were obtained with a 2-oxabicyclo[3.2.0]heptan-6-one: Dawson, M. J.; Lawrence, G. C.; Lilley, G.; Todd, M.; Noble, D.; Green, S. M.; Roberts, S. M.; Wallace, T. W.; Newton, R. F.; Carter, M. C.; Hallet, P.; Paton, J.; Reynolds, D. P.; Young, S. *J. Chem. Soc., Perkin Trans 1* **1983**, 2119.

(10) Ghosez, L.; Montaigne, R.; Roussel, A.; Vanlierde, H.; Mollet, P. *Tetrahedron* **1971**, *27*, 615.

(11) (a) Racemic monochloro ketones **16** and **18** are represented in the schemes by the structures of the single 6*S*-enantiomers. It is understood that each compound is actually a 1:1 mixture of 6*R* and 6*S* components. (b) Monochloro ketones **16** and **18** were mentioned in earlier work, but no synthesis and few spectral details were given: Roberts, S.; Dieffenbacher, A.; Dreiding, A. S. *Helv. Chim. Acta* **1970**, *53*, 417.

(12) See Experimental Section, General Remarks.

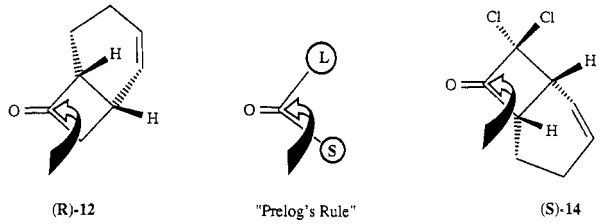


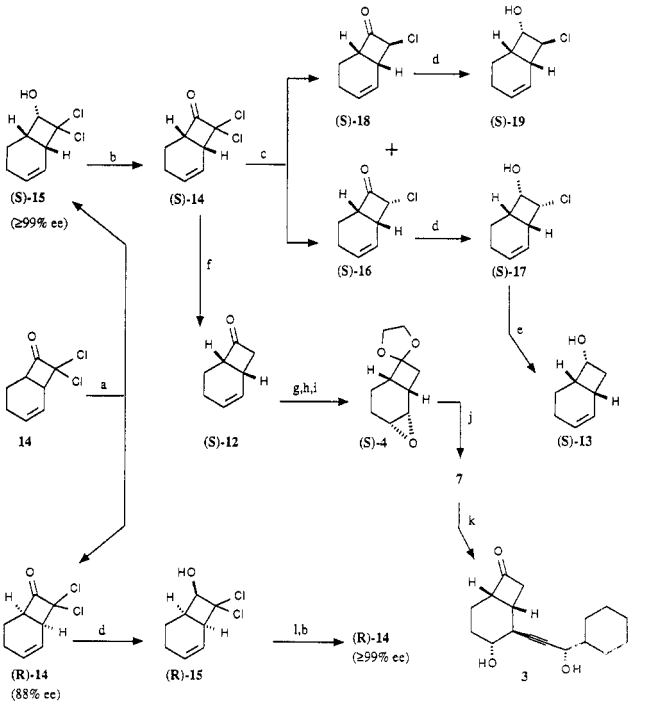
Figure 1. Reduction by bakers' yeast from the exo-*re* face of ketones (*R*)-**12** and (*S*)-**14**.

markably complete enantioselectivity and a dramatic acceleration in rate relative to the other substrates.

Thus, the yeast-mediated reduction of racemic 8,8-dihydro ketone **12** gave 6*R* endo-alcohol (*R*)-**13**[13] (92% ee, 25% yield) and 6*S*-enriched ketone (*S*)-**12** (40% ee, 32% yield) after a 90-h reaction time. Conversely, 8,8-dichloro ketone **14** gave 6*S*-dichloro endo-alcohol (*S*)-**15** (100% ee, 27% yield) and 6*R* ketone (*R*)-**14** (82% ee, 14% yield), isolated after a reaction time of 45 min. The reduction of monochloro ketone **16** also gave a 6*S* alcohol but this reaction was not nearly as selective, affording cis-endo-chlorohydrin (*S*)-**17** of 56% ee (17% yield) and slightly enriched ketone (*R*)-**16** (12% ee, 67% yield) after 6 h. The course of the reductions was in accord with "Prelog's rule", which states that a yeast hydride equivalent is generally delivered from the *re* face of a ketone, as determined by the relative steric bulk of the α-substituents.[14] The major alcohol product in each case then derived from the single ketone enantiomer for which reduction from the exo face also satisfied this rule. It is evident that the steric influence of the C-6 ring junction in determining the formation of a 6*R* alcohol product from ketone **12** was overwhelmed by the influence of the 8,8-dichloride system in ketone **14**, whereas the single endo-chloride substituent in **16** had an intermediate effect (Figure 1).[15]

It is probable that the extraordinary enantioselectivity of reduction observed with dichloro ketone **14** was determined mostly by the steric influence of the exo-chloride substituent, with little contribution by the endo-chloride, and a similar selectivity might be expected from the yeast treatment of exo-monochloride **18**. However, **18** was not available in sufficient quantities to test this hypothesis.[16] Steric factors cannot explain the remarkable speed of reduction of **14** with bakers' yeast, which was uncharacteristically fast for a microbial reaction.[17] The reduction rate must reflect a particularly favorable combination of polarity and lipophilicity for the dichlorocyclobutanone substructure in terms of interaction of the 6*S* enantiomer

Scheme III. Synthesis of Correlation Compounds[a]



[a] (a) Bakers' yeast; (b) PCC; (c) Zn/HOAc/20 °C; (d) $NaBH_4$; (e) Bu_3SnH; (f) Zn/HOAc/80 °C; (g) $HOCH_2CH_2OH$, H^+; (h) *N*-bromoacetamide; (i) K_2CO_3, H_2O; (j) **6**, *n*-BuLi, $BF_3{\cdot}Et_2O$, −78 °C; (k) H_3O^+; (l) hexane recrystallization.

with the appropriate yeast enzyme. In the same context, the low yield of enriched 6*R* ketone relative to 6*S* alcohol noted in yeast reductions of **14** implies that dichloro ketone 6*R* enantiomer (*S*)-**14** may be readily degradable by an alternate metabolic route.

The 6*S*-dichloro alcohol (*S*)-**15** was crystalline and was judged to be optically pure directly as isolated from the yeast reduction because further recrystallization did not increase its optical rotation. Reduction of crude 6*R* ketone (*R*)-**14** with $NaBH_4$ gave the 6*R*-dichloro alcohol (*R*)-**15** (88% ee), which was also a solid, and a single recrystallization afforded material of 99% ee as judged by optical rotation. Optical purities of ≥99% ee for the enantiomeric alcohols (*S*)-15 and (*R*)-15 were verified by NMR experiments using chiral europium shift reagents. Optically pure (*S*)-**15** ($[\alpha]_D$ −217.1°) was used to prepare the standards by which the relative stereochemistry and optical purity of all other yeast reduction products were judged, by comparing the signs and magnitudes of optical rotations. Synthesis of the correlation standards and proofs of the assigned configurations are discussed in the following section.

Correlations of Relative and Absolute Stereochemistry. Optically pure correlation compounds were prepared from (*S*)-**15** as follows (Scheme III). Oxidation of (*S*)-**15** with pyridinium chlorochromate (PCC) gave 6*S*-dichloro ketone (*S*)-**14**, and reduction of (*S*)-**14** with zinc and acetic acid at 80 °C then gave 6*S* 8,8-dihydro ketone (*S*)-**12**. A milder zinc reduction of (*S*)-**14** gave 6*S* endo-monochloro ketone (*S*)-**16** and some of the corresponding exo-monochloro ketone (*S*)-**18**. Reduction of a mixture of (*S*)-**16** and (*S*)-**18** with $NaBH_4$ gave the 6*S*-cis-endo-chlorohydrin (*S*)-**17** and trans isomer (*S*)-**19**, and further treatment of (*S*)-**17** with tributyltin hydride afforded the 6*S*-dihydro alcohol (*S*)-**13**.

The single alcohol products of the yeast reductions were intuitively designated as 7-endo-alcohols, but a rigorous

(13) The prescripts *R* and *S* used in the reference numbering of most of the chiral bicyclooctane derivatives described in this paper refer to the assignments at bridgehead carbon C-6 (C-7 in the case of epoxide **4**), which most accurately describe the absolute configuration of the whole molecule. Similarly, the prescripts 6*R* and 6*S* used in the trival names of compounds (e.g., 6*S* alcohol) refer to the absolute configuration at bridgehead carbon C-6 and not to the position of the functional group named.

(14) Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119.

(15) Following the completion of our work, a finding of similar substrate and product enantioselectivity was reported for reductions of 7-*endo*-chloro- and 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-ones with isolated enzyme systems. The cited work was accomplished by incubation of the ketones with 3α,20β-hydroxy steroid alcohol dehydrogenase and yeast alcohol dehydrogenase in the presence of reduced nicotinamide adenine dinucleotide: Davies, G. H.; Gartenmann, C. C.; Leaver, J.; Roberts, S. M.; Turner, M. K. *Tetrahedron Lett.* **1986**, *27*, 1093.

(16) Attempts to prepare **18** by the epimerization of endo-chloride **16** under acid or base catalysis and in the presence of chloride salts were not successful.

(17) Reaction times of 36–72 h are generally reported for reductions of ketones with bakers' yeast. For an example, see: Seebach, D.; Sutter, M. A.; Weber, R. H.; Züger, M. F. *Org. Synth.* **1984**, *63*, 1. See also ref 2a–d and references therein.

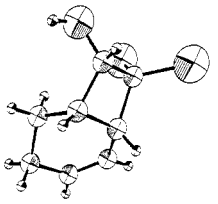


Figure 2. X-ray structure of (*S*)-**15**, ORTEP representation.

proof required the availability of corresponding diastereomers, preferably the corresponding 7-exo-alcohols, for the required NMR spectral comparisons. Reductions of the racemic ketones with hydride reagents were therefore carried out, with the expectation that the desired 7-exo-alcohols would be produced as isolable (if minor) byproducts. However, the surprisingly complete exo-face specificity of reduction of these ketones observed with yeast was observed with chemical hydride reagents as well. Thus, the reactions of **12**, **14**, and **16** with $NaBH_4$ gave single products which were in each case the racemic alcohol with the same endo configuration at C-7 as obtained with yeast. Reduction with LAH also failed to give any detectable exo-alcohol product from ketone **12**. The reason for the apparent inaccessibility of the endo face of bicyclo[4.2.0]octenones relative to the bicyclo[3.2.0]heptenone system was not completely obvious from the study of Dreiding models. However, it is evident that the puckered twist-boat conformations assumed by the cyclohexene ring in these systems result in an effective steric blockade to underside attack of the carbonyl group.[18]

A solution to the problem of firmly assigning 7-endo-alcohol structures to (*S*)-**13** and (*S*)-**17** was provided through the availability of the trans chlorohydrin byproduct (*S*)-**19**. Thus, comparative studies of ^{13}C NMR spectra and of NOE effects in the proton spectra of the trans-8-exo-chloro 7-endo-alcohol (*S*)-**19** and the cis-8-endo-chloride isomer (*S*)-**17** allowed the unequivocal assignment of relative stereoisomerism to the pair. The upfield shifts of C-2, C-7, and C-8 in the ^{13}C spectrum of (*S*)-**17** relative to that of (*S*)-**19** indicated that the chloride of (*S*)-**17** was cis to both C-2 and the hydroxyl group at C-7, whereas the equivalent shifts of the C-5's indicated that the configuration of the hydroxyl group was the same in both samples. After the proton connectivities in the ^1H NMR spectra of (*S*)-**17** and (*S*)-**19** were assigned through spin–spin decoupling, NOE difference experiments were carried out. Saturation of the H-8 signal in the spectrum of (*S*)-**17** showed enhancements on the resonances for H-1, H-6, and H-7, while saturation of H-7 enhanced the resonances on H-1, H-6, and H-8, which demonstrated that all four of these protons were on the same side of the molecule. The same experiments with the spectrum of (*S*)-**19** showed that saturation of H-7 caused enhancements only on H-1 and H-6, while saturation of H-8 had no effect on H-1, H-6, or H-7, supporting the assigned trans structure. This work confirmed the 7-endo-hydroxyl assignments for (*S*)-**17** and (*S*)-**19**, and also established the structure of the unsubstituted endo-alcohol (*S*)-**13** which had been prepared from (*S*)-**17**. A single-crystal X-ray analysis of the 6*S*-dichloro alcohol (*S*)-**15** established the endo-hydroxyl

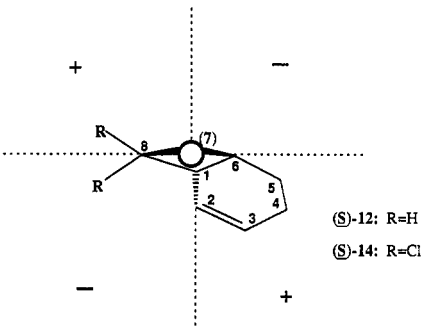


Figure 3. Octant projection of 6*S*-ketones.

structure for this compound (Figure 2), but the data was insufficient for an assignment of absolute stereochemistry.[19]

Circular dichroism (CD) spectra and Cotton curves were then measured for optically pure samples of 6*S*-dichloro ketone (*S*)-**14** and 6*S*-dihydro ketone (*S*)-**12**, and in addition for the 6*R*-dichloro ketone (*R*)-**14** prepared by oxidation of 6*R* alcohol (*R*)-**15** with PCC. Ketones (*S*)-**12** and (*S*)-**14** showed positive Cotton effects and (*R*)-**14** showed a negative effect essentially equal in magnitude to that of (*S*)-**14**. Examination of Dreiding models of the 6*S* ketones showed the cyclohexene ring to reside in one positive octant while all other effects cancelled out (Figure 3), so that conclusions of absolute stereochemistry based on the Cotton effects confirmed the predictions of "Prelog's rule".

The yeast-mediated resolution of dichloro ketone **14** appeared to be the method of choice for preparation of the 6*S*-bicyclo[4.2.0]octane system. The final test of the assignment of 6*S* stereochemistry to the dichloro alcohol (*S*)-**15** and of its practicality as a synthetic intermediate was accomplished through a synthesis of the advanced intermediate keto diol **3**, whose stereochemistry had been determined unequivocally by correlation with a compound of known absolute configuration.[5] Thus, 6*S* ketone (*S*)-**12** (prepared from (*S*)-**15**) was converted into the 7*S* ketal endo-epoxide (*S*)-**4** via a bromohydrin intermediate by sequential treatment with ethylene glycol and β-naphthalenesulfonic acid, *N*-bromoacetamide, and aqueous potassium carbonate.[20] The BF_3–etherate-catalyzed addition of the lithium salt of 3*S* propargyl alcohol TBDMS ether **6** to (*S*)-**4** gave ketal silyl ether **7**, and deprotection with aqueous acid then afforded the desired keto diol **3**. The signs and magnitudes of the optical rotation and Cotton effect in the CD spectrum of **3** were identical with those measured for **3** prepared by our earlier synthesis,[5] confirming assignment of the desired "natural" stereochemistry to resolved (*S*)-**15**.

Summary

Resolution of dihydro ketone **12** via the yeast reduction of dichloro ketone **14** has proven ideally suited to the large-scale synthesis of prostacyclin analogue **1** (RS-93427-007) by virtue of the reversal of enantioselectivity provided by the removable 8,8-dichloride substituents, the speed of reaction, the ease of attaining an optically pure intermediate, and the accessibility and low cost of the critical "reagent". The 6*S*-dichloro alcohol (*S*)-**15** has been

(18) The use of computer-aided molecular modeling and MMP2 force field calculations indicate that the cyclohexene rings of bicyclo[3.2.0]-oct-2-en-7-ones can exist in either of two stable pseudo-boat conformations differing in energy by approximately 1 kcal. The endo approach to the carbonyl group in these conformers is partially blocked either by an axial proton (endo H-4 or H-5) or by a part of the cyclohexene ring itself. Similar steric factors are not present in the case of the bicyclo-[3.2.0]heptenone system, wherein the fused cyclopentene ring is completely planar. McDowell, B.; Kertesz, D. J., unpublished results.

(19) The structure shown is one of three unique almost identical molecules found within the unit cell. Sublimation of the sample during the analysis prevented the collection of sufficient data for an assignment of absolute configuration.

(20) The product (*S*)-**4** actually contained ca. 20% of the corresponding exo-epoxide, as discussed in ref 5, the inseparable mixture being used in the following step without untoward effect.

prepared in single batch fermentations using up to 1 kg of **14**, and the byproduct 6*R* ketone (*R*)-**14** has found utility in the enantioselective preparation of "ent-15-epi" prostacyclin analogues such as **2**. It is expected that the strategy of manipulating powerful yet transformable directing systems comparable to the present α-dihalo ketone substructure will find increasing application in the synthesis of chiral intermediates through biocatalytic means.

Experimental Section

General Remarks. Proton NMR spectra were determined at 300 MHz, and carbon-13 NMR spectra were recorded at 75.5 MHz. Determinations of enantiomeric excess by ^{1}H NMR employed the chiral shift reagent Eu(HFC)$_3$. Circular dichroism data were measured at Stanford University and the University of California at Berkeley. The X-ray structural determination was done by Oneida Research Services, Inc., Whitesboro, NY. Analytical TLC was performed with Analtech 2.5 cm × 10 cm × 0.25 cm silica GF plates, and flash chromatography[21] was carried out with 230–400-mesh silica gel (E. Merck). The removal of solvent from volatile materials was performed with a rotary evaporator and a bath temperature of 30 °C or less. Active bakers' yeast manufactured by either Red Star or Molino Mills was purchased in normal food stores, and both brands gave equivalent results. "Nutritional yeast" is a form of cooked yeast sold in bulk by Red Star for use as a food supplement. The conventions for numbering the positions in compounds were the same as those used in our previous work.[5]

Reductions of 8,8-Dichlorobicyclo[4.2.0]oct-2-en-7-one (14) with Zinc. A. Preparation of Bicyclo[4.2.0]oct-2-en-7-one (12). To a stirred solution of dichloro ketone **14**[22] (105 g, 0.55 mol) in acetic acid (700 mL) was added approximately 1 equiv of zinc dust (36 g, 0.55 mol) in small portions over 1 h, with occasional cooling by ice bath to keep the temperature under 30 °C. When the exotherm had subsided, more zinc dust (144 g, 2.2 mol) was added, and the mixture was heated at 80 °C for 5 h. The mixture was cooled and filtered through Celite, the cake being washed with acetic acid, and the filtrate was diluted with water and extracted three times with CH_2Cl_2. The extracts were washed with dilute aqueous $NaHCO_3$ and water and then dried over Na_2SO_4, and the solvent was removed under reduced pressure to give 60 g (89%) of **12** as a yellow liquid. The reaction workup could also be performed as described in the next example. The ^{1}H NMR spectrum of **12** was identical with that of optically enriched (*S*)-**12**, for which data is reported.

B. Preparation of 8-*endo*-Chlorobicyclo[4.2.0]oct-2-en-7-one (16) and 8-*exo*-Chlorobicyclo[4.2.0]oct-2-en-7-one (18). Zinc dust (1.5 g, 23 mmol) was added in portions to a stirred solution of **14** (1.5 g, 7.8 mmol) in acetic acid (12 mL) over 15 min, the temperature of the mixture being maintained at 18 °C by cooling in a water bath. The mixture was stirred for another 10 min and was then filtered through a cake of Celite made up in hexane, the filter cake then being washed with hexane. The filtrate was further diluted with hexane and water, and the organic layer was separated, washed 3× with water, and dried over Na_2SO_4. Removal of the solvent by evaporation under vacuum gave 1.08 g of an oil shown by TLC (5% acetone–hexane) to consist mainly of endo-chloride **16** (R_f 0.27) containing a small amount of exo-chloride **18** (R_f 0.50), but with no detectable **12** (R_f 0.63) being present. Separation of the mixture by flash chromatography (2.5% acetone–hexane) afforded 0.67 g (54.5%) of pure **16** and 105 mg of crude **18**. A portion of **16** was distilled (70–80 °C at 0.1 Torr) for analysis: IR ($CHCl_3$) 1790 cm^{-1}; ^{1}H NMR δ 1.60 (m, 1 H, H-5a), 2.00–2.17 (m, 3 H, H-4's, H-5b), 3.27 (m, 1 H, H-1), 3.64 (m, 1 H, H-6), 5.00 (dd, 1 H, $J_{8,1}$ = 9.1 Hz, $J_{8,6}$ = 2.3 Hz, H-8), 5.79 (m, 1 H, H-2), 6.05 (m, 1 H, H-3); ^{13}C NMR δ 18.24 (C-5), 20.83 (C-4), 30.10 (C-1), 53.16 (C-6), 62.73 (C-8), 123.12 (C-2), 131.41 (C-3), 202.63 (C-7); MS, *m/e* 156, 158 (M^+); HRMS, *m/e* calcd for C_8H_9ClO (M^+) 156.0342, found 156.0337. It was difficult to achieve the appearance of complete purity for exo-chloro ketone **18** as judged by TLC.[23a] Crude **18** was purified by chromatography on Florisil (1% acetone–hexane) and again by flash chromatography on silica gel (2% Et_2O–4% CH_2Cl_2–hexane), affording 40 mg (3.3%) of pure **18**: IR ($CHCl_3$) 1790 cm^{-1}; ^{1}H NMR δ 1.81 (m, 2 H, H-5's), 2.02 (m, 2 H, H-4's), 2.94 (m, 1 H, H-1), 3.77 (m, 1 H, H-6), 4.42 (dd, 1 H, $J_{8,1}$ = 4.8 Hz, $J_{8,6}$ = 2.9 Hz, H-8), 6.03 (m, 2 H, H-2, H-3); ^{13}C NMR δ 19.73 (C-5), 21.34 (C-4), 35.71 (C-1), 54.64 (C-6), 66.48 (C-8), 125.16 (C-2), 130.85 (C-3), 203.40 (C-7); MS, *m/e* 156,158 (M^+); HRMS, *m/e* calcd for C_8H_9ClO (M^+) 156.0342, found 156.0340. The upfield shifts of C-1, C-2, and C-8 in the ^{13}C NMR spectrum of **16** relative to that of **18** indicate that the chloride substituent of **16** is cis to C-2, confirming the assigned endo structure. Further evidence for the assignments was obtained from NOE difference experiments. Thus, saturation of either H-1 or the H-6 signal in the ^{1}H NMR spectrum of **16** caused enhancement of the H-8 signal, indicating that these protons are on the same side of the molecule, while saturation of the corresponding signals in the spectrum of **18** caused no similar enhancements. The magnitudes of the ^{1}H coupling constants for **16** and **18** are in agreement with the published values.[11b]

Reductions with Bakers' Yeast. A. Preparation of (1*R*,6*S*)-Bicyclo[4.2.0]oct-2-en-7-one [(*S*)-12] (Optically Enriched) and (1*S*,6*R*,7*R*)-Bicyclo[4.2.0]oct-2-en-7-ol [(*R*)-13] (Optically Enriched). To a stirred mixture of active bakers' yeast (25 g) and nutritional yeast (2.5 g) in tap water (475 mL) maintained at 32 °C was added a solution of ketone **12** (3.0 g, 24.6 mmol) in ethanol (25 mL) followed by sucrose (1 g). Extra quantities of yeast (20 g), nutritional yeast (3.5 g), and sucrose (2.5 g) were added in portions over the next 24 h, with the emission of bubbles of CO_2 being noted only for short periods after the addition of sucrose. The mixture was maintained at 28–32 °C for 90 h, after which TLC analysis (20% EtOAc–hexane) indicated that the conversion of **12** (R_f 0.54) to (*R*)-**13** (R_f 0.24) had essentially stopped. The mixture was centrifuged, and the supernatent was decanted from the yeast cake and was extracted several times with EtOAc. The yeast cake was stirred in acetone and then filtered through Celite, the cake being further washed with acetone. The combined yeast cake filtrates were reduced to a low volume by evaporation at reduced pressure and then diluted with EtOAc, and the resulting aqueous layer was separated and discarded. Supernatent extracts and yeast extracts were combined, and the solvent was removed at reduced pressure, affording 5.0 g of a brown oil. Separation of the crude product mixture by flash chromatography (18% EtOAc–hexane increasing to 50% EtOAc–hexane) afforded (*S*)-**12** and (*R*)-**13**, both of which still contained a polar impurity. The polar material which coeluted with the products was later isolated and identified by ^{1}H NMR as oleic acid, apparently extracted from the yeast. Ketone (*S*)-**12** was purified by Kugelrohr distillation (40–70 °C at 0.1 Torr), which gave 0.95 g (32%) of material appearing to be >95% pure by TLC. Two further microdistillations and a chromatography (3% acetone–hexane) gave a sample of (*S*)-**12** for analysis: $[\alpha]^{25}_D$ +68.4° (*c* 0.35, $CHCl_3$); 40% ee (calcd vs the rotation of optically pure (*R*)-**12**); IR ($CHCl_3$) 1780 cm^{-1}; ^{1}H NMR δ 1.57 (m, 1 H, H-5a), 1.91–2.11 (m, 3 H, H-4's, H-5b), 2.60 (m, 1 H, H-8a), 2.93 (m, 1 H, H-1), 3.28 (m, 1 H, H-8b), 3.57 (m, 1 H, H-6), 5.87 (m, 1 H, H-3), 5.96 (m, 1 H, H-2); ^{13}C NMR δ 19.56 (C-5), 21.31 (C-4), 23.04 (C-1), 52.16 (C-8), 57.46 (C-6), 128.50 (C-3), 128.96 (C-2), 211.78 (C-7); MS, *m/e* 140 (MNH_4^+). Crude alcohol (*R*)-**13** was subjected to two further flash chromatographies (first using 3% acetone–CH_2Cl_2, then 7% Et_2O–CH_2Cl_2), which gave 0.75 g (25%) of pure material. A sample was distilled (70 °C at 1 Torr) for analysis: $[\alpha]^{25}_D$ +108.2° (*c* 0.42, $CHCl_3$); 89% ee calcd vs $[\alpha]_D$ of optically pure (*S*)-**13** (92% ee by chiral shift ^{1}H NMR); ^{1}H NMR δ 1.63 (s, 1 H, OH), 1.63–1.99 (m, 4 H, H-4a, H-5's, H-8a), 2.08 (m, 1

(21) Performed according to the procedure of: Still, W. C.; Kuhn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(22) Prepared as described by: Corey, E. J.; Ravindranathan, T. *Tetrahedron Lett.* **1971**, 4753. See also ref 10.

(23) The following problems were encountered in handling chloro ketones, whether racemic or optically enriched. (a) Chloro ketones **14** and **18** appeared to be particularly unstable to TLC grade silica gel, and even analytically pure samples streaked badly on TLC. (b) Chloro ketones stained much less intensely with ammonium molybdate than did the corresponding alcohols, which led to low TLC estimates of their concentrations in mixtures. (c) Early measurements of $[\alpha]^{25}_D$ values for optically enriched samples of **14** were inconsistant, possibly due to instability of all but the purest material in $CHCl_3$ solution. Comparison of rotations for the derived alcohols (*R*)-**15** and (*S*)-**15** was taken to be a more reliable measure of enantiomeric excess.

H, 4-Hb), 2.26 (m, 1 H, H-1), 2.49–2.69 (m, 2 H, H-6, H-8b), 4.31 (dt, 1 H, J's = 7.7 Hz, H-7), 5.70 (m, 1 H, H-2), 5.82 (m, 1 H, H-3); ^{13}C NMR δ 19.16, 22.11 (C-4, C-5), 40.02 (C-8), 40.16 (C-6), 65.54 (C-7), 128.21, 129.35 (C-2, C-3); MS, *m/e* 124 (M^+); HRMS, *m/e* calcd for $C_8H_{12}O$ (M^+) 124.0888, found 124.0886. The exo-alcohol corresponding to (*R*)-**13** was not found among the minor byproducts.

B. Preparation of (1*S*,6*R*)-8,8-Dichlorobicyclo[4.2.0]-oct-2-en-7-one ((*R*)-14) (Optically Enriched) and (1*R*,6*S*,7*S*)-8,8-Dichlorobicyclo[4.2.0]oct-2-en-7-ol ((*S*)-15) (Optically Pure). A mixture of bakers' yeast (170 g), nutritional yeast (17 g), and sucrose (10 g) in water (3.6 L) was maintained at 33 °C in a mechanically stirred 4-L resin kettle warmed by a mantle. A solution of ketone **14** (23.8 g, 0.125 mol) in ethanol (170 mL) was added dropwise over 15 min, followed by addition of a further portion of sucrose (6 g). A TLC analysis (eluted twice with 10% acetone–hexane) of the mixture 30 min after completion of the addition showed the starting material **14** (R_f 0.73) to be largely replaced by the alcohol (*S*)-**15** (R_f 0.34).[23b] After 45 min of reaction time the mixture was centrifuged in four portions to precipitate the yeast, and the workup was completed as described in the previous example, affording 23.3 g of brown oil as the crude product. A portion of optically pure alcohol (*S*)-**15** [4.0 g, $[\alpha]^{25}_D$ −216° (*c* 0.69, $CHCl_3$)] crystallized directly from a solution of the crude product in hexane (100 mL). The mother liquor materials were purified by flash chromatography (5% acetone–hexane gradually increasing to 100% acetone) affording 4.5 g (19%) of >90% pure ketone (*R*)-**14** as a yellow oil and 4.8 g of crude (*S*)-**15**, which contained considerable amounts of oleic acid (see previous example). Crystallization of the crude (*S*)-**15** from hexane gave another 2.4 g of optically pure (*S*)-**15**. The combined yield of (*S*)-**15** was 6.4 g (27%) of white needles: mp 86–87 °C; $[\alpha]^{25}_D$ −217.1° (*c* 0.62, $CHCl_3$); ≥99% ee (vide infra); ^{1}H NMR δ 1.68 (m, 2 H, H-5's), 1.89 (m, 1 H, H-4a), 2.14 (m, 1 H, H-4b), 2.69 (d, 1 H, *J* = 10.6 Hz, OH), 2.83 (m, 1 H, H-6), 3.18 (m, 1 H, H-1), 4.70 (dd, 1 H, *J* = 10.3, 8.6 Hz, H-7), 5.78 (m, 1 H, H-2), 6.10 (m, 1 H, H-3); ^{13}C NMR δ 17.59 (C-4), 21.85 (C-5), 35.88 (C-6), 45.76 (C-1), 78.14 (C-7), 92.26 (C-8), 121.61 (C-3), 132.07 (C-2); MS, *m/e* 210, 212 (MNH_4^+). Anal. Calcd for $C_8H_{10}OCl_2$: C, 49.76; H, 5.22; Cl, 36.73. Found: C, 50.00; H, 5.32; Cl, 36.84. Proton NMR employing $Eu(HFC)_3$ detected only a single enantiomer in this material, and the $[\alpha]^{25}_D$ was not increased by further recrystallizations. Crude ketone (*R*)-**14** was purified by a further flash chromatography (1.5% acetone–hexane), which gave 3.4 g (14.2%) of pure material, a portion of which was distilled by Kugelrohr (70–90 °C at 0.1 Torr) to give a sample for analysis: $[\alpha]^{25}_D$ −76.2° (*c* 0.41, $CHCl_3$); 87% ee (calcd vs the rotation of optically pure (*R*)-**14**); IR ($CHCl_3$) 1800 cm^{-1}; ^{1}H NMR δ 1.67 (m, 1 H, H-5a), 2.00–2.19 (m, 3 H, H-4's, H-5b), 3.46 (m, 1 H, H-1), 4.12 (m, 1 H, H-6), 5.88 (m, 1 H, H-2), 6.10 (m, 1 H, H-3); ^{13}C NMR δ 18.81 (C-4), 20.86 (C-5), 44.28 (C-1), 53.37 (C-6), 86.74 (C-8), 123.04 (C-3), 132.42 (C-2), 196.61 (C-7); MS, *m/e* 190,192 (M^+). Anal. Calcd for $C_8H_8OCl_2$: C, 50.29; H, 4.22, Cl, 37.12. Found: C, 50.18; H, 4.56; Cl, 36.76. Ketone (*R*)-**14** was judged to be 88% ee, calculated by comparing the $[\alpha]^{25}_D$ of the $NaBH_4$ reduction product alcohol (*R*)-**15** (vide infra) with that of optically pure (*S*)-**15**.[23c] An exo-alcohol corresponding to (*S*)-**15** could not be found in the minor column fractions or mother liquor materials.

C. Preparation of (1*S*,6*R*,8*S*)-8-Chlorobicyclo[4.2.0]oct-2-en-7-one ((*R*)-16) (Slightly Enriched) and (1*R*,6*S*,7*S*,8*R*)-8-Chlorobicyclo[4.2.0]oct-2-en-7-ol ((*S*)-17) (Optically Enriched). A solution of endo-monochloro ketone **16** (785 mg, 5.01 mmol) in ethanol (8 mL) and sucrose (350 mg) were added to a magnetically stirred suspension of bakers' yeast (7 g) and nutritional yeast (700 mg) in water (150 mL) maintained at 34 °C. A TLC analysis (12% EtOAc–hexane) after 6 h indicated that over half of the starting material (R_f 0.39) had been converted to the corresponding alcohol (*S*)-**17** (R_f 0.32).[23b] The mixture was stored at 4 °C for 16 h, after which workup according to the previous examples gave the crude product mixture as a yellow oil. Flash chromatography (4% EtOAc–14% CH_2Cl_2–hexane) followed by careful removal of the solvents at reduced pressure gave 530 mg of ketone (*R*)-**16** (67.5%) and 130 mg of alcohol (*S*)-**17** (16.4%), both of which were homogeneous by TLC. The lack of oleic acid in these samples probably resulted from having performed a particularly underloaded chromatography. Distillation of a portion of ketone (*R*)-**16** afforded a colorless liquid: $[\alpha]^{25}_D$ +2.2° (*c* 0.37, $CHCl_3$); 12% ee (calcd vs the $[\alpha]^{25}_D$ of optically pure (*S*)-**16**); ^{1}H NMR spectrum and TLC behavior identical with those of racemic **16**. Distillation of (*S*)-**17** gave a waxy solid: mp 34–36 °C; $[\alpha]^{25}_D$ −104.4° (*c* 0.26, $CHCl_3$); 56% ee (calcd vs $[\alpha]^{25}_D$ of optically pure (*S*)-**17**); ^{1}H NMR δ 1.66–1.99 (m, 3 H, H-4a, H-5's), 2.20 (m, 1 H, H-4b), 2.72 (m, 1 H, H-6), 2.96 (m, 1 H, H-1), 4.55 (dd, 1 H, J's = 6.5 Hz, H-7), 4.73 (ddd, 1 H, *J* = 6.4, 6.3, 2.7 Hz, H-8), 5.63 (m, 1 H, H-2), 6.08 (m, 1 H, H-3); ^{13}C NMR δ 19.51 (C-5), 21.95 (C-4), 33.43 (C-1), 39.18 (C-6), 63.75 (C-8), 67.93 (C-7), 123.57 (C-2), 131.49 (C-3); MS, *m/e* 158, 160 (M^+); HRMS, *m/e* calcd for $C_8H_{11}OCl$ (M^+) 158.0498, found 158.0497. No 7-exo-alcohol corresponding to (*S*)-**17** was found in the reaction mixture.

Optically Pure Products from Enriched 6*R*-Dichloro Ketone ((*R*)-14). A. (1*S*,6*R*,7*R*)-8,8-Dichlorobicyclo-[4.2.0]oct-2-en-7-ol ((*R*)-15). To a solution of the optically enriched dichloro ketone yeast reduction product (*R*)-**14** (275 mg, 1.44 mmol) in methanol (8 mL) at 0 °C was added $NaBH_4$ (30 mg, 3.17 mequiv) in portions over 5 min. After another 10 min EtOAc and water were added to the mixture and the organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated to dryness under vacuum, giving a white solid. Flash chromatography of the crude product (12% EtOAc–hexane) and evaporation of the proper fractions gave 205 mg (74%) of enriched alcohol (*R*)-**15**: mp 82–85 °C; $[\alpha]^{25}_D$ +178° (*c* 0.47, $CHCl_3$); 82% ee (calcd against the $[\alpha]^{25}_D$ of optically pure (*S*)-**15**). In another preparation, enriched (*R*)-**14** (2.50 g, 13.1 mmol) was reduced with $NaBH_4$ (300 mm, 31.7 mequiv) in methanol (50 mL), and the reaction was worked up as described above. The crude product was not chromatographed in this case, but was recrystallized directly from hexane (25 mL), affording 1.57 g (62.2%) of pure (*R*)-**15**: mp 85–86 °C; $[\alpha]^{25}_D$ +214.4° (*c* 0.47, $CHCl_3$); ≥99% ee (chiral shift ^{1}H NMR); all other data identical with those recorded for (*S*)-**15**. The mother liquor materials were chromatographed and minor byproducts were examined carefully, but no trace of a 7-exo alcohol corresponding to (*R*)-**15** was found.

B. (1*S*,6*R*)-8,8-Dichlorobicyclo[4.2.0]oct-2-en-7-one ((*R*)-14). A stirred mixture of optically pure (*R*)-**15** (200 mg, 1.05 mmol), pyridinium chlorochromate (PCC) (460 mg, 2.14 mmol), and anhydrous $MgSO_4$ (760 mg, 6.3 mmol) in CH_2Cl_2 (12 mL) was heated at reflux for 5 h, after which the reaction was judged complete by TLC. The mixture was filtered slowly through a cake of Florisil (80 mL) made up in Et_2O, and the cake was further washed with Et_2O. The filtrate was reduced to a low volume by evaporation under vacuum, and the crude product was then purified by flash chromatography (3% acetone–hexane). The pure product was distilled (55 °C at 0.1 Torr), giving 85 mg (43%) of ≥99% ee (*R*)-**14** for analysis: $[\alpha]^{25}_D$ −87.8° (*c* 0.36, $CHCl_3$); θ −12 530 (λ_{max} 322.6 nm, CH_3OH); TLC behavior and ^{1}H NMR spectrum identical with those reported for enriched (*R*)-**14**.

Optically Pure Standards from 6*S*-Dichloro Alcohol ((*S*)-15). A. (1*R*,6*S*)-8,8-Dichlorobicyclo[4.2.0]oct-2-en-7-one ((*S*)-14). The oxidation of optically pure (*S*)-**15** (4.0g, 20.7 mmol) with PCC (9.2g, 42.7 mmol) in CH_2Cl_2 (200 mL) containing $MgSO_4$ (14g, 117 mmol) and a workup utilizing a Florisil filtration were carried out as described in the previous example. Distillation of the crude product by Kugelrohr (60–80 °C at 0.1 Torr) afforded 3.1 g (78%) of (*S*)-**14** as a colorless, apparently pure liquid. However, a slight exotherm followed by formation of turbidity and worsening of the TLC of the sample was noted shortly after the distillation, probably due to a side reaction catalyzed by some remaining PCC-related impurity. The material was repurified by flash chromatography (3% acetone–hexane) affording 2.40 g (61%) of pure and stable ≥99% ee (*S*)-**14**, a portion of which was distilled for analysis: $[\alpha]^{25}_D$ +91.2° (*c* 0.48, $CHCl_3$); θ +12960 (λ_{max} 322.8, CH_2Cl_2); all other data identical with those reported for enriched (*R*)-**14**.

B. (1*R*,6*S*)-Bicyclo[4.2.0]oct-2-en-7-one ((*S*)-12). Optically pure dichloro ketone (*S*)-**14** (1.10 g, 5.76 mmol) was reduced with zinc dust (2.0 g, 30.6 mmol) in acetic acid (10 mL) at 80 °C according to the procedure described for preparation of racemic **12**. Kugelrohr distillation of the rather volatile product (65 °C at 12 Torr) gave 0.50 g (46%) of ≥99% ee (*S*)-**12**: $[\alpha]^{25}_D$ +171.40 (*c* 0.47, $CHCl_3$); θ +6586 (λ_{max} 298.3 nm, CH_3OH); MS, *m/e* 122 (M^+); HRMS, *m/e* calcd for $C_8H_{10}O$ (M^+) 122.0732, found 122.0731; other data were as described for enriched (*S*)-**12**.

C. (1*R*,6*S*,8*R*)-8-Chlorobicyclo[4.2.0]oct-2-en-7-one ((*S*)-16) and (1*R*,6*S*,8*S*)-8-Chlorobicyclo[4.2.0]oct-2-en-7-one ((*S*)-18). Optically pure dichloro ketone (*S*)-**14** (830 mg, 4.34 mmol) was reduced with zinc dust (570 g, 8.7 mmol) in acetic acid (8 mL) under the mild conditions described for the reduction of racemic **14**, affording 610 mg of crude product as an oil. A portion of the product mixture (210 mg) was separated by flash chromatography (2% acetone–hexane). The more polar product was 168 mg (72%) of endo-chloro ketone (*S*)-**16**: $[\alpha]^{25}_D$ −18.5° (*c* 0.40, $CHCl_3$). The less polar product was 11 mg (4.7%) of exo-chloro ketone (*S*)-**18**: $[\alpha]^{25}_D$ +83.1° (*c* 0.35, $CHCl_3$). The compounds were identical with the corresponding racemic compounds by TLC behavior and ^1H NMR spectra.

D. (1*R*,6*S*,7*S*,8*R*)-8-Chlorobicyclo[4.2.0]oct-2-en-7-ol ((*S*)-17) and (1*R*,6*S*,7*S*,8*S*)-8-Chlorobicyclo[4.2.0]oct-2-en-7-ol ((*S*)-19). A portion of the crude mixture of monochloro ketones isolated from the zinc reduction of (*S*)-**14** described in the preceding procedure (400 mg, 2.55 mmol) was not further purified, but was treated with $NaBH_4$ (60 mg, 6.4 mequiv) in methanol (8 mL) at 0 °C for 10 min. A TLC analysis (2% Et_2O in 1:1 CH_2Cl_2–hexane) showed the product mixture to consist mostly of (*S*)-**17** (R_f 0.31) containing some (*S*)-**19** (R_f 0.22). Isolation and flash chromatography of the crude product in the same solvent system afforded 242 mg (54% from (*S*)-**14**) of (*S*)-**17** and 24 mg (5.3% from (*S*)-**14**) of (*S*)-**19**. Cis-chlorohydrin (*S*)-**17** was a waxy solid: mp 48–50 °C; $[\alpha]^{25}_D$ −185.1° (*c* 0.42, $CHCl_3$); ^1H NMR identical with those described for enriched (*S*)-**17**. The trans-chlorohydrin (*S*)-**19** was semicrystalline at room temperature: $[\alpha]^{25}_D$ −169.1° (*c* 0.28, $CHCl_3$); ^1H NMR δ 1.57 (m, 1 H, H-5a), 1.75–2.00 (m, 2 H, H-4a, H-5b), 2.10 (H, 1 H, H-4b), 2.40 (m, 1 H, H-1), 2.73 (m, 1 H, H-6), 3.92 (dd, 1 H, *J* = 7.9 Hz, H-8), 4.29 (dd, 1 H, *J* = 8.4, 7.1 Hz, H-7), 5.82–5.97 (m, 2 H, H-2, H-3); ^{13}C NMR δ 19.47 (C-5), 22.18 (C-4), 35.42 (C-6), 36.38 (C-1), 65.50 (C-7), 125.35 (C-2), 130.24 (C-3); MS, *m/e* 158, 160 (M^+); HRMS, *m/e* calcd for $C_8H_{11}OCl$ (M^+) 158.0498, found 158.0497. A comparison of NOE effects in the ^1H NMR spectra of these compounds is described in the text.

E. (1*R*,6*S*,7*R*)-Bicyclo[4.2.0]oct-2-en-7-ol ((*S*)-13). Azobis(isobutyronitrile) (10 mg, 0.06 mmol) was added to a solution of optically pure endo-chlorohydrin (*S*)-**17** (197 mg, 1.24 mmol) and tri-*n*-butyltin hydride (0.66 mL, 2.5 mmol) in hexane (10 mL), and the mixture was then heated at reflux under strong lighting. A TLC (3% Et_2O–CH_2Cl_2) after 16 h showed that all starting material (R_f 0.51) had been replaced by (*S*)-**13** (R_f 0.28). The solvent was removed under reduced pressure and flash chromatography (3% Et_2O–CH_2Cl_2) of the residue then gave 110 mg (71.4%) of nearly pure (*S*)-**13**. A sample of (*S*)-**13** was rechromatographed in the same system and then distilled (70 °C, 1 Torr) for analysis: $[\alpha]^{25}_D$ −121.4° (*c* 0.52, $CHCl_3$); ^1H NMR and TLC behavior identical with those that of optically enriched (*R*)-**13**.

Intermediates in the Synthesis of Prostacyclin Analogue 1. A. (1*S*,2*S*,4*R*,7*S*)-Spiro(3-oxatricyclo[5.2.0.0^{2,4}]nonane-8,2′-[1,3]dioxolane) ((*S*)-4). A solution of optically pure ketone (*S*)-**12** (450 mg, 3.68 mmol), ethylene glycol (1.5 mL) and β-naphthalenesulfonic acid (10 mg) in benzene (20 mL) was prepared in a flask fitted with a 50-mL addition funnel filled with activated 4-Å seives and topped with a reflux condenser. The mixture was heated in a 90 °C bath for 2 h, during which the reflux of condensate through the seives effected continuous removal of water. The mixture was cooled, diluted with EtOAc, washed with dilute aqueous $NaHCO_3$ followed by water, dried over Na_2SO_4, and concentrated to 3 mL by evaporation under vacuum. The solution of crude ketal was diluted with acetone (15 mL) and water (7 mL), and the mixture was cooled to 0 °C in an ice bath, after which *N*-bromoacetamide (650 mg, 4.7 mmol) was added in portions over 1 h. The mixture was then stirred at 20 °C for 16 h, after which K_2CO_3 (1.5 g) was added, and stirring was continued for another 48 h. The solution was diluted with water and extracted twice with CH_2Cl_2, after which the extracts were washed with water, dried over Na_2SO_4, and concentrated under vacuum. Flash chromatography (9% acetone–hexane) of the crude product gave 450 mg (67%) of (*S*)-**4**, which was homogeneous by TLC:[20] $[\alpha]^{25}_D$ −9.5° (*c* 0.47, $CHCl_3$); ^1H NMR identical with that previously reported for racemic material.[5]

B. (3′*S*,1*S*,2*S*,3*R*,6*S*)-2-(3′-Cyclohexyl-3′-hydroxyprop-1′-ynyl)-3-hydroxybicyclo[4.2.0]octan-7-one (3). A solution of the *S*-propargyl alcohol silyl ether **6** (0.94 g, 3.71 mmol) (for preparation, see ref 5) in dry THF (20 mL) was prepared in a 50-mL two-neck flask equipped with a septum and an atmosphere of dry argon. The flask was cooled in an ice bath, and a solution of 1.21 M *n*-butyllithium in hexane (2.76 mL, 3.34 mmol) was added. After stirring at 0 °C for 15 min the mixture was cooled to −78 °C, and a solution of epoxide (*S*)-**4** (450 mg, 2.47 mmol) in THF (5 mL) was added. After 10 min, boron trifluoride etherate (0.32 mL, 2.47 mmol) was added dropwise by syringe. A TLC analysis (1.5% acetone–CH_2Cl_2, eluted twice) after 90 min showed that all epoxide (*S*)-**4** (R_f 0.40) had been replaced by **7** (R_f 0.55) as the major product. Saturated aqueous sodium sulfate (5 mL) was added, and the mixture was warmed to 20 °C, diluted with ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated to dryness under vacuum, yielding a yellow oil. The product was purified by flash chromatography (1.5% acetone–CH_2Cl_2), affording 668 mg (62%) of **7** as a colorless oil: $[\alpha]^{25}_D$ 0° (*c* 0.40, $CHCl_3$). A portion of ketal silyl ether **7** (400 mg, 0.92 mmol) was dissolved in a mixture of acetonitrile (15 mL) and aqueous 0.5 N H_2SO_4 (6 mL), and the solution was stirred for 16 h at 20 °C under a nitrogen atmosphere. The solution was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized from acetone–hexane, affording 228 mg (89.6%) of pure **3** in two crops: colorless needles, mp 133–135 °C; $[\alpha]^{25}_D$ +60.0° (*c* 0.41, $CHCl_3$); θ +1470 (λ_{max} 296.8 nm, CH_3OH); IR (KBr) 1775 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 74.08; H, 8.75. These data and the ^1H NMR spectrum were identical with those previously reported for a sample of **3** prepared via a classic resolution.[5]

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Registry No. **1**, 105284-21-7; **3**, 105803-42-7; (*S*)-**4**, 115224-53-8; **6**, 105803-39-2; **7**, 105803-40-5; (±)-**12**, 52466-03-2; (*S*)-**12**, 52466-04-3; (*S*)-**12** ethylene ketal, 115224-54-9; (*R*)-**13**, 115304-29-5; (*S*)-**13**, 115304-31-9; (±)-**14**, 115304-27-3; (*R*)-**14**, 115224-50-5; (*S*)-**14**, 115224-52-7; (*R*)-**15**, 115224-51-6; (*S*)-**15**, 115150-89-5; (±)-**16**, 115246-87-2; (*R*)-**16**, 115304-32-0; (*S*)-**16**, 115304-30-8; (*S*)-**17**, 115246-88-3; (±)-**18**, 115304-28-4; (*S*)-**18**, 115304-79-5; (*S*)-**19**, 115304-80-8.