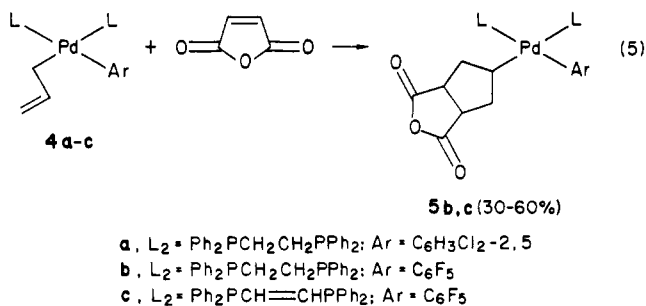


Figure 1. Molecular structure of **5c**. Non-hydrogen atoms are represented by thermal ellipsoids at the 30% probability level.

not separately evaluate k_4 for each olefin, this value most probably increases as the electron-withdrawing ability of olefinic substituents increases. This notion is consistent with the higher reactivity in the spontaneous reductive elimination of $\text{Pd}(\eta^3\text{-C}_3\text{H}_5)(\text{Ar})(\text{ER}_3)$ ($\text{E} = \text{P}, \text{As}$) containing the more electron-withdrawing ligand (ER_3).⁵ It should also be noted that the rate constant extrapolated at 0 °C from the kinetic parameters⁵ for this spontaneous process of $\text{Pd}(\eta^3\text{-C}_3\text{H}_5)(\text{Ar})[\text{P}(\text{OPh})_3]$, the most reactive among those examined,⁵ is only $1.6 \times 10^{-2} \text{ h}^{-1}$. Thus, comparison of this value with k_1 in Table I may provide a good indication of signifying the effectiveness (k_4) of π -acidic olefin coordination in the C-C coupling, especially when apparently very small values of k_3/k_{-3} for each olefin¹¹ are taken into account.

Next we examined the reaction of η^1 -allyl complexes **4**¹² with olefins. Spontaneous reductive elimination of **4a** proceeded more slowly than that of **1** to give a good yield of the coupling product. However, allyl chloride and dimethyl maleate did not accelerate this reaction or alter the reaction course (see below). Reductive elimination of other Pd complexes that contain only η^1 -bound organic ligands (e.g., PdMe_2L_2) has also been shown to be unaffected by π -acidic olefins.¹³ With the more acidic olefin, i.e., maleic anhydride, **4** underwent a different reaction course in CH_2Cl_2 at 0 °C to result in rapid formation of comparable amounts of propene and complexes **5**,¹⁴ the first Pd-containing, formal [2 + 3] cycloadducts¹⁵ (eq 5).



(11) We failed to detect **3** by ^1H NMR spectra during olefin-promoted reductive elimination.

(12) Numata, S.; Okawara, R.; Kurosawa, H. *Inorg. Chem.* **1977**, *16*, 1737.

(13) (a) Ozawa, F.; Ito, T.; Nakamura, Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1868. (b) Komiya, S.; Akai, Y.; Tanaka, K.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1985**, *4*, 1130.

(14) Characterized by elemental analysis and ^1H NMR spectra.

(15) Rosenblum, M. *Acc. Chem. Res.* **1974**, *7*, 122.

Only one isomeric cycloadduct was obtained, as revealed by ^1H NMR analysis of reaction mixtures. The structure of **5c** was determined by X-ray crystallography (Figure 1).¹⁶ The mutually trans orientation of the metal and the carbonyl substituents with respect to the C_5 ring is opposite to the cis orientation in the [2 + 4] cycloadduct of $\text{Fe}(\eta^5\text{-C}_5\text{H}_5)(\eta^1\text{-C}_5\text{H}_5)(\text{CO})_2$ and maleic anhydride.^{17,18}

The results described in this study demonstrated for the first time that formation of a four-coordinated olefin complex is a prerequisite to the facile reductive elimination of ally complexes of Pd. This is in sharp contrast to reductive elimination from five-coordinated organo(olefin)nickel(II) complexes.^{13b,20} The present study also suggests that the allyl-Pd bond should be subjected to highly π -acidic olefins preferably in the η^3 -bound form, at least prior to the formation of the active intermediate.²¹

Supplementary Material Available: Table of fractional atomic coordinates and temperature factors for **5c** (3 pages). Ordering information is given on any current masthead page.

(16) Crystal data: $\text{C}_{30}\text{H}_{30}\text{F}_5\text{O}_3\text{P}_2\text{Pd}$, $M_r = 809.0$, triclinic, space group $P\bar{1}$, $a = 9.526(3) \text{ \AA}$, $b = 14.218(5) \text{ \AA}$, $c = 14.122(5) \text{ \AA}$, $\alpha = 70.47(3)^\circ$, $\beta = 96.48(3)^\circ$, $\gamma = 92.64(3)^\circ$, $Z = 2$, $D_c = 1.500 \text{ g cm}^{-3}$, $\mu(\text{Mo K}\alpha) = 6.66 \text{ cm}^{-1}$. Intensity data were collected by the θ - 2θ scan technique with a 2θ value up to 54° on a Rigaku automated, four-circle diffractometer using graphite-monochromatized Mo $K\alpha$ radiation. The structure was solved by the heavy-atom method and refined anisotropically by block-diagonal least-squares procedure. The final R factor is 0.054 for 6277 ($F_o > 3\sigma(F_o)$) reflections.

(17) Wright, M. E. *Organometallics* **1983**, *2*, 558.

(18) Equation 5 may have proceeded via direct attack of maleic anhydride at the C=C bond,¹⁵ or initial coordination of this olefin to Pd, followed by its insertion into the Pd-C bond.¹⁹ The precise pathway that is consistent with the observed stereochemistry is currently under investigation.

(19) Calligaris, M.; Carturan, G.; Nardin, G.; Scrivanti, A.; Wojcicki, A. *Organometallics* **1983**, *2*, 865.

(20) McKinney, R. J.; Roe, D. C. *J. Am. Chem. Soc.* **1985**, *107*, 261.

(21) Efficient coupling of palladium(η^3 -allyl)₂ induced by olefins^{1b,c} may have proceeded via conversion of palladium(η^3 -allyl)₂(olefin) to an intermediate of type palladium(η^3 -allyl)(η^1 -allyl)(olefin).

An Asymmetric Simmons-Smith Reaction

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Herein we report a new method of asymmetric cyclopropanation¹ that we believe has considerable potential in organic synthesis. The new process, outlined in Scheme I, appears to offer special advantages including high efficiency, procedural simplicity, predictable chirality of the product, and mildness of the reaction conditions.

When an α,β -unsaturated acetal dissolved in hydrocarbon was treated with excess methylene iodide and diethylzinc,² the corresponding cyclopropane was obtained in a reasonable yield with high diastereoselectivity. The acetal group was readily transformed to the aldehyde ($p\text{-TsOH-H}_2\text{O}$) or to the ester (ozonolysis).³ Several examples of this new process are given in Table I. Since both (*R,R*)- and (*S,S*)-tartaric acid esters are readily available in optically pure form,⁴ this method allows the synthesis of both

(1) Asymmetric cyclopropanation of α,β -unsaturated carbonyl derivatives: (a) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1968**, *90*, 6852; **1973**, *95*, 7418. (b) Johnson, C. R.; Barbachyn, M. R. *Ibid.* **1982**, *104*, 4290. (c) Abdallah, H.; Cree, R.; Carrie, R. *Tetrahedron Lett.* **1982**, *23*, 503.

(2) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53.

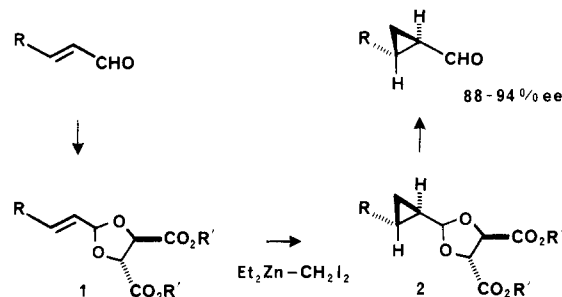
(3) Deslongchamps, P.; Atlani, P.; Frehel, D.; Malaval, A.; Moreau, C. *Can. J. Chem.* **1974**, *52*, 3651.

Table I. Asymmetric Simmons-Smith Reaction^a

entry	acetal	conditions, °C, h	product	yield, ^b %	% de ^c (% ee)	confign	[α] _D , deg (c) ^d
1	R ¹ , Me, R ² , <i>i</i> -Pr	-20, 1; 0, 4	R ¹ , Me, R ² , <i>i</i> -Pr	90	94 (92) ^e	<i>R,R</i> ^e	-56.1 (1.10)
2	<i>n</i> -Pr, Et	-20, 3	<i>n</i> -Pr, Et	95	88		-45.8 (1.26)
3	<i>n</i> -Pr, <i>i</i> -Pr	-20, 1; 0, 5	<i>n</i> -Pr, <i>i</i> -Pr	80	91		-49.3 (1.05)
4	Ph, Et	-20, 6; 0, 6	Ph, Et	91	87 (92) ^f	<i>R,R</i> ^f	-94.8 (1.03)
5	Ph, <i>i</i> -Pr	-20, 1; 0, 3	Ph, <i>i</i> -Pr	92	91	<i>R,R</i> ^f	-84.5 (0.98)
6		-20, 5		94	89		47.3 (1.02)
7		-20, 1; 0, 4		81	89		-43.6 (0.97)
8		-20, 7; 20, 10		61	88 ^g		-44.8 (1.13)
9		-20, 7; 20, 10		50	85 ^g		15.6 (1.00)

^a All the reactions were performed as described in text. ^b Isolated pure product. All products have been characterized by analytical and spectral data. ^c Diastereomeric excess (de). Unless otherwise specified, the diastereoselectivity was determined by ¹H NMR analysis of the product and/or the corresponding acetal of (2*R*,4*R*)-2,4-pentanediol. Thus, a base-line separation of the two doublets (or singlets) of CH(OR)₂ was obtained in the presence of the shift reagent, Eu(fod)₃ (90 or 60 MHz), or in the absence of the shift reagent (500 MHz). ^d In ethanol. ^e The absolute configuration has been proven by transformation to (1*R*,2*R*)-2-methylcyclopropanecarboxylic acid: [α]_D²⁴ -71.9° (c 1.00, ethanol); reference value of 1*R*,2*R* isomer: [α]_D¹⁹ -39.7° (ethanol) (51% ee): Sugita, T.; Inouye, Y. *Bull. Chem. Soc. Jpn.* 1966, 39, 1075. ^f The absolute configuration has been proven by transformation to (1*R*,2*R*)-2-phenylcyclopropanecarboxylic acid: [α]_D²⁶ -287.6° (c 1.21, ethanol); reference value of 1*S*,2*S* isomer: [α]_D²² +311.7° (c 1.776, 1 dm, ethanol): Inouye, Y.; Sugita, T.; Walborsky, H. M. *Tetrahedron* 1964, 20, 1695. ^g The diastereomeric ratio and absolute configuration were tentatively assigned by ¹H NMR spectra (CDCl₃) of the corresponding aldehyde after mild hydrolysis. The CHO of axial aldehyde, δ 8.66 ppm; the CHO of equatorial aldehyde, δ 8.59 ppm. (CHO of *trans*-4-*tert*-butylcyclohexanecarbaldehyde, δ 9.61; the corresponding *cis* isomer, δ 9.70. Accrombessi, G.; Geneste, P.; Olive, J. L.; Pavia, A. A. *Bull. Soc. Chim. Fr.* 1981, II-19.

Scheme I



enantiomers of cyclopropanes from α,β-unsaturated aldehydes in a predictable manner. Generally the acetal from diisopropyl tartrate (DIPT) gave a slightly higher enantiomeric excess than that of diethyl tartrate (DET). Entries 8 and 9 indicated that the asymmetric induction is totally controlled by the auxiliary tartrate ligand and is independent of the chirality of the isopropenyl group. It should also be noted that a single isomer of the starting

acetal was formed from dialkyl tartrate which has C₂ symmetry, thus avoiding troublesome separation of diastereoisomers.

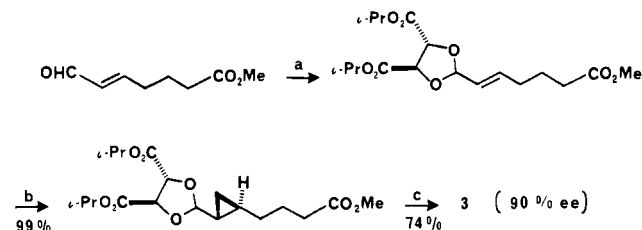
A representative procedure for the asymmetric cyclopropanation follows. To a solution of the acetal 1, R = Ph, R' = Et (6.4 g, 20 mmol),⁵ in dry hexane (220 mL) was added diethylzinc (100 mmol, 32.3 mL of a 3.1 M hexane solution)⁶ at -20 °C. Methylene iodide (16.2 mL, 0.20 mol) was added dropwise to the resulting stirred solution and the mixture was vigorously stirred at -20 °C for 6 h and 0 °C for 6 h.⁷ The reaction mixture was poured into cold aqueous ammonium chloride and the product was extracted with ether repeatedly. The ether layers were washed with sodium thiosulfate and water. The combined ether layers were dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel afforded the pure cyclopropane 2, R = Ph, R' = Et, as a colorless oil (6.08 g, 91%): [α]_D²⁵ -94.2°

(5) The preparation of acetal 1 is as follows: The mixture of cinnamaldehyde, triethyl orthoformate (1.2 equiv), and a catalytic amount of ammonium nitrate in ethanol was stirred at room temperature for 4 h to give the corresponding diethyl acetal. A mixture of the crude acetal, L-(+)-diethyl tartrate (1.1 equiv), and a catalytic amount of pyridinium tosylate in benzene was heated to remove ethanol for 1.5 h. After usual workup followed by recrystallization from hexane, the acetal 1 was obtained as colorless crystals (63% yield): mp 55.5–56.0 °C.

(6) We are grateful to Toyo Stauffer Chemical Co., Ltd., for generous gift of diethylzinc.

(7) Vigorous mechanical stirring is very important during these operations; otherwise the reaction sometimes occurs explosively. See ref 2.

(4) Recent asymmetric syntheses using dialkyl tartrate: (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* 1980, 102, 5976. (b) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H.; *Ibid.* 1982, 104, 7667. See also: (c) Seebach, D. In "Modern Synthetic Methods 1980"; Scheffold, D., Ed.; Otto Salle Verlag: Frankfurt.

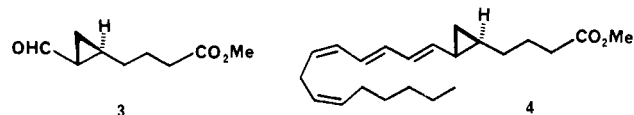
Scheme II^a

^a (a) (1) HC(OEt)₃-EtOH, NH₄NO₃, 78%, (2) L-(+)-DIPT, TsOH-Py 50%; (b) CH₂I₂-Et₂Zn; (c) TsOH, MeOH-H₂O.

(c 1.03, EtOH); IR (neat) 3000 (s), 2960 (m), 1755 (s), 1620 (m), 1380 (m), 1160 (w), 870 (w), 760 (m); ¹H NMR (CCl₄) δ 0.67-1.87 (m, 3 H), 1.27, 1.30 (2 t, *J* = 8 Hz, 3 H each), 1.87-2.37 (m, 1 H), 4.20 (q, *J* = 8 Hz, 4 H), 4.47-4.67 (m, 2 H), 5.03 (d, *J* = 5.6 Hz, 1 H), 7.07 (br s, 5 H, Ar H). Anal. Calcd for C₁₈H₂₂O₆: C, 64.7; H, 6.6. Found: C, 64.7; H, 6.6.⁸

The observed selectivity is ascribed to the high affinity of the zinc reagent for ethereal oxygen. Complex formation between the oxygen atom and the organozinc reagent, followed by methylene transfer to the nearest face of the neighboring double bond, has been proposed to account for the stereoselectivity and the large rate enhancement found for methylene addition to allylic alcohols and ethers relative to simple olefins.^{9,10}

It seems clear that the method described herein will be useful for the production of a wide range of chiral cyclopropanes, an increasingly important class of biologically active functionalities. One attractive initial target was the aldehyde 3, a key intermediate in synthesis of 5,6-methanoleukotriene A₄ (4), a stable and selective



inhibitor of leukotriene biosynthesis.¹¹ An enantioselective synthetic route of 3 is shown in Scheme II.¹²

Acknowledgment. Financial supports from the Ministry of Education, Japanese Government, and generous gift sample from Ono Pharmaceutical Co. are acknowledged.

(8) The acetal group was transformed to the aldehyde or to the carboxylic acid as follows: A mixture of the acetal 2 (1.67 g, 5.0 mmol) and *p*-TsOH (1.0 g) in THF-water (50 mL-10 mL) was heated at reflux for 7 h. Usual workup followed by column chromatography on silica gel gave a colorless oil (450 mg, 62%): bp (bath temp) 120 °C (1 torr); [α]_D²⁵ -378° (c 0.374, CHCl₃), [α]_D²⁵ -340° (c 0.363, CHCl₃); ¹H NMR (CCl₄) δ 1.17-2.77 (m, 4 H), 7.10 (m, 5 H), 9.33 (d, *J* = 3.8 Hz, 1 H); IR (neat) 3040 (w), 2850 (w), 2730 (w), 1695 (s), 1170 (m), 760 (m), 700 (m) cm⁻¹. Similarly the acetals 5 and 6 (entry 8 and 9 of Table I) were transformed to the corresponding aldehydes on treatment with *p*-TsOH in ethanol-water (1:1) at room temperature for 2-5 days in 75-79% yields. A solution of the acetal 2 (1.67 g, 5.0 mmol) in CCl₄ (50 mL) was oxidized with excess ozone at 0 °C for 5 h. The solvent was evaporated in vacuo and the residue was dissolved in ethyl acetate and washed with brine. The separated organic layers were dried over sodium sulfate and concentrated in vacuo. The residue was dissolved in EtOH-10 N KOH (25 mL-5 mL) and the mixture was stirred at 0 °C for 2 h to complete the hydrolysis of the ester. The mixture was poured in cold 2 N HCl and the product was extracted with ethyl acetate repeatedly. After drying and concentration of the organic layers, the product was purified by column chromatography on silica gel to give 2-phenylcyclopropanecarboxylic acid as a colorless liquid (0.435 g, 43% in two steps overall yield); see legend f of Table I. Similarly the ozonolysis of the acetal of entry 3, Table I, gave the corresponding ester in 67% yield.

(9) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, 20, 1.

(10) Poulter, C. D.; Friedrich, E. C.; Winstein, S. *J. Am. Chem. Soc.* **1969**, 91, 6892.

(11) Nicolaou, K. C.; Petasis, N. A.; Seitz, S. P. *J. Chem. Soc., Chem. Commun.* **1981**, 1195.

(12) Stereochemical purity (90% ee) of the product was determined by the following conversion: Treatment of 6 with (2*R*,4*R*)-2,4-pentandiol and pyridinium tosylate in benzene at reflux for 1 h gave the corresponding acetal (87% yield): [α]_D²⁷ -51.2° (c 1.05, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 4.31 (d, *J* = 5.65 Hz, CH(OR)₂); the *S* isomer δ 4.35 (d, *J* = 5.65 Hz).

Homochiral Ketals in Organic Synthesis. Diastereoselective Cyclopropanation

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The modern synthetic chemist often plans an *asymmetric* synthesis of a complex target molecule. Incorporation of one or more protecting groups is usually an integral part of this plan. Although the number of available protecting groups has grown as the complexity of target molecules has increased, on the whole protecting groups remain unidimensional: they protect, nothing more.¹ This situation is unfortunate given the time and effort devoted to their manipulation. Development of methodology for asymmetric synthesis based on incorporation of *homochiral protecting groups* would seem both logical and economical.^{2,3} We have embarked on such a developmental program, and herein report that homochiral cycloalkenone ketals undergo efficient and diastereoselective cyclopropanation when treated with the Simmons-Smith reagent.^{4,5}

Treatment of 2-cyclohexen-1-one ketal **1**⁶ (2.5 mmol) with freshly prepared zinc-copper couple⁷ (1.63 g), methylene iodide (8 mmol), and a crystal of iodine in refluxing diethyl ether gave, after 1 h and in 90-98% chemical yield, a 9:1 mixture of diastereomeric cyclopropanes **2a** and **2b**,⁶ as determined by 62.9-MHz ¹³C NMR spectroscopy.⁸ This ratio was confirmed and the identity of the major diastereomer established by hydrolysis⁹ of the diastereomeric mixture to (1*R*,6*S*)-bicyclo[4.1.0]heptan-2-one, [α]_D²⁵ +12.7° (c 3.4, CHCl₃), the rotation of which corresponds to 83% optical purity.^{5a,c} Most encouragingly, 2-cyclopenten-1-one ketal **3** and 2-cyclohepten-1-one ketal **5** gave similar results.^{9,10}

(1) Green, T. W. "Protective Groups in Organic Synthesis"; Wiley: New York, 1981.

(2) Recently, diastereoselective β-addition reactions of homochiral acetals and ketals have been described; see: (a) Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1984**, 106, 5004-5005. (b) Fukutani, Y.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1984**, 5911-5912. (c) Ghribi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, 3083-3086.

(3) Other synthetic uses for homochiral acetals and ketals have been described; see: (a) Elliott, J. D.; Steele, J.; Johnson, W. S. *Tetrahedron Lett.* **1985**, 2535-2538 and previous articles in the series. (b) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, 4581-4584. (c) Sekizaki, H.; Jung, M.; McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, 104, 7372-7374.

(4) For reviews of the Simmons-Smith reaction, see: (a) Furukawa, J.; Kawabata, N. In "Advances in Organometallic Chemistry"; Stone, F. G. A., West, R., Ed.; Academic Press: New York, 1974; Vol. 12, Chapter 3. (b) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1972**, 20, 1-131.

(5) Previous uses of the Simmons-Smith reaction to produce homochiral cyclopropanes include: (a) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1982**, 104, 4290-4291. (b) Lightner, D. A.; Jackman, D. E. *Tetrahedron Lett.* **1975**, 3051-3054. (c) Hill, R. K.; Morgan, J. W. *J. Org. Chem.* **1968**, 33, 927-928. (d) Sawada, S.; Oda, J.; Inouye, Y. *J. Org. Chem.* **1968**, 33, 2141-2143. (e) Sawada, S.; Takehana, K.; Inouye, Y. *J. Org. Chem.* **1968**, 33, 1767-1770.

(6) All yields refer to isolated and purified compounds. Satisfactory NMR and HRMS data were obtained for all compounds.

(7) Shank, R. S.; Shechter, H. *J. Org. Chem.* **1959**, 24, 1825-1826.

(8) Authentic diastereomeric mixtures of compounds **2**, **4**, **6**, **12**, and **16** were prepared for spectroscopic comparison by direct ketalization of the corresponding racemic cyclopropyl ketones with 1,4-di-*O*-benzyl-L-threitol. For previous examples of the use of ¹³C NMR in determining diastereomer ratios, see: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183-2186.

(9) Conditions for hydrolysis: 3% aqueous sulfuric acid, THF, room temperature, 3.5 h. Recovered (1*R*,6*S*)-bicyclo[4.1.0]heptan-2-one (83% yield) was spectroscopically and chromatographically identical with racemic material prepared by cyclopropanation of 2-cyclohexen-1-one (ref 4b, p 85). 1,4-Di-*O*-benzyl-L-threitol was also recovered. Similarly, hydrolysis of cyclopropane ketal **6** gave bicyclo[5.1.0]octan-2-one, [α]_D²⁵ +25.7° (c 0.53, CDCl₃) in 75% yield, hydrolysis of **8** gave 1-methylbicyclo[4.1.0]heptan-2-one, [α]_D²⁵ -19.4° (c 0.90, CDCl₃), in 81% yield, and hydrolysis of **12** gave 1-acetylbicyclo[4.1.0]heptane, [α]_D²⁶ -86.8° (c 0.37, CDCl₃), in 86% yield, the rotation of which corresponds to 93% optical purity (see ref 5a).

(10) The identities of the major diastereomers for the bicyclo[3.1.0]hexanone and bicyclo[5.1.0]octanone systems are assumed to be **4a** and **6a** in analogy with the observed preferential formation of **2a** from 2-cyclohexen-1-one ketal **1**. Work is currently in progress to confirm this assumption.