picrate salts in the presence and absence of host by the method described earlier[5a] and later made more precise.[5d,e] Table I records the results based on the UV absorbance of the picrate ion in the $CDCl_3$ layer, except for those of 2,3-naphtho-18-crown-6 and 2,6-pyrido-18-crown-6. The R, K_a, and $-\Delta G°$ values for those hosts binding Li^+ were based on UV absorbances in the $CDCl_3$ layers, but for the other ions it was based on absorbances measured on the water layer.[5d,e] The values for 1,3-benzo-18-crown-6 measured previously are included in Table I for comparison purposes. Cyclic 2,6-pyrido-18-crown-6 was prepared earlier,[4c] but its K_a values for the picrates are reported here for the first time.

Registry No.—**1**, 18803-11-7; **2**, 18593-19-6; **3**, 69928-10-5; **4**, 69928-11-6; **5**, 69928-12-7; **6**, 68669-11-4; **7**, 69928-13-8; **8**, 69928-14-9; **9**, 69928-15-0; **9**·K·picrate, 69942-22-9; **9**·Rb·picrate, 69942-24-1; **9**·Cs·picrate, 69942-26-3; **9**·NH_4·picrate, 70131-36-1; **9**·Li·picrate, 69961-17-7; **9**·Na·picrate, 69961-15-5; **10**, 69928-16-1; **10**·Li·picrate, 69942-28-5; **10**·Na·picrate, 69942-30-9; **10**·K·picrate, 69942-32-1; **10**·Rb·picrate, 69942-34-3; **10**·Cs·picrate, 69942-36-5; **10**·NH_4·picrate, 70131-37-2; **11**, 69928-17-2; **11**·Li·picrate, 69942-38-7; **11**·Na·picrate, 69942-40-1; **11**·K·picrate, 69942-42-3; **11**·Rb·picrate, 69942-44-5; **11**·Cs·picrate, 69961-13-3; **11**·NH_4·picrate, 70145-48-1; **12**, 69928-18-3; **12**·Na·picrate, 69942-46-7; **12**·Li·picrate, 69942-48-9; **12**·K·picrate, 69942-50-3; **12**·Rb·picrate, 69942-52-5; **12**·Cs·picrate, 69942-54-7; **12**·NH_4·picrate, 70131-38-3; **13**, 69928-19-4; **13**·K·picrate, 69942-56-9; **13**·Rb·picrate, 69942-58-1; **13**·Cs·picrate, 69942-60-5; **13**·NH_4·picrate, 70131-39-4; **13**·Li·picrate, 69942-62-7; **13**·Na·picrate, 69942-64-9; **14**, 69928-20-7; **14**·Li·picrate, 69942-66-1; **14**·Na·picrate, 69942-68-3; **14**·K·picrate, 69942-70-7; **14**·Rb·picrate, 69942-72-9; **14**·Cs·picrate, 69942-74-1; **14**·NH_4·picrate, 70145-46-9; **16**, 69928-21-8; **16**·Li·picrate, 69942-76-3; **16**·Na·picrate, 69942-78-5; **16**·K·picrate, 69942-80-9; **16**·Rb·picrate, 69942-82-1; **16**·Cs·picrate, 69942-84-3; **16**·NH_4·picrate, 70145-50-5; **17**, 69928-22-9; **18**, 69928-23-0; **18**·Li·picrate, 69942-86-5; **18**·Na·picrate, 69942-88-7; **18**·K·picrate, 69942-89-8; **18**·Rb·picrate, 69942-91-2; **18**·Cs·picrate, 69942-93-4; **18**·NH_4·picrate, 70131-40-7; **19**, 53914-89-9; **19**·Li·picrate, 69942-95-6; **19**·Na·picrate, 69942-97-8; **19**·K·picrate, 69942-98-9; **19**·Rb·picrate, 69943-00-6; **19**·Cs·picrate, 69943-02-8; **19**·NH_4·picrate, 70131-41-8; **20**·Li·picrate, 64799-51-5; **20**·Na·picrate, 64799-49-1; **20**·K·picrate, 64851-30-5; **20**·Rb·picrate, 64822-96-4; **20**·Cs·picrate, 64799-34-4; **20**·NH_4·picrate, 64916-33-2; **21**·Li·picrate, 69943-04-0; **21**·Na·picrate, 69943-06-2; **21**·K·picrate, 69943-07-3; **21**·Rb·picrate, 69943-08-4; **21**·Cs·picrate, 69928-25-2; **21**·NH_4·picrate, 70131-35-0; 2-bromotoluene, 95-46-5; phenylphosphonic dichloride, 824-72-6; tetraethylene glycol, 112-60-7; ethylene glycol, 107-21-1; bis[2-(((2-hydroxyethoxy)methyl)phenyl)phenyl]-phosphine oxide, 69928-26-3; phosphorus oxychloride, 10025-87-3; 2-(2′-bromophenyl)-4,4-dimethyloxazoline, 69928-27-4; bis(*o*-tolyl)phosphinyl chloride, 59472-84-3; 2-(1*H*)-tetrahydropyrimidone, 1852-17-1; hexaethylene glycol ditosylate, 42749-27-9.

References and Notes

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Reduction of Cyclopropyl Halides. Stereochemistry of the Lithium Aluminum Deuteride Reduction of *r*-1-Chloro-*c*- and -*t*-2-methyl-2-phenylcyclopropane[1]

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The lithium aluminum deuteride reduction of *r*-1-chloro-*c*- and -*t*-2-methyl-2-phenylcyclopropane (**3a** and **2a**) in dimethoxyethane (DME) at 100 °C was shown to give a single deuterated isomer of 1-methylphenylcyclopropane (**4**). The isomer of **4** formed was found to be **4b** by ^1H NMR spectral comparison with an authentic sample of **4b** prepared by a stereospecific route. A mechanism for the $LiAlD_4$ reduction is given to account for the stereochemical results.

The reduction of *gem*-dihalocyclopropanes with lithium aluminum hydride ($LiAlH_4$) proceeds in a stepwise fashion to give monohalocyclopropanes and cyclopropanes.[2] Debromination of *gem*-bromofluorocyclopropanes with $LiAlH_4$ in refluxing tetrahydrofuran (THF) proceeds with complete retention of configuration.[3] The dechlorination of *gem*-chlorofluorocyclopropanes with $LiAlH_4$ in diglyme at 100 °C proceeds stereoselectively with predominant retention of

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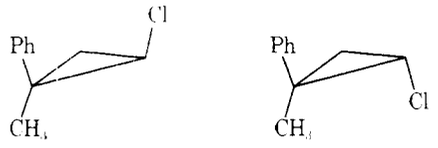
Table I. Product Distribution in the Reduction of 1a with Varying Amounts of $LiAlH_4$ in DME at 100 °C

mole ratio of $LiAlH_4$–1	% product distribution[a]					reaction time, h
	1a	3a	2a	4a	5	
2:1	24.5	29.6	39.5	3.8	2.5	48–50
3:1	trace	35.9	53.6	7.5	3.0	48–50
4:1		29.1	53.4	14.4	3.0	48–50
5:1		23.3	43.8	27.3	5.6	48–50
5:1		5.1	38.5	48.9	7.6	72

[a] Determined by VPC analysis, ref 22.

configuration. However, nonbonded interactions have been invoked to explain one example where inversion predominates.[4]

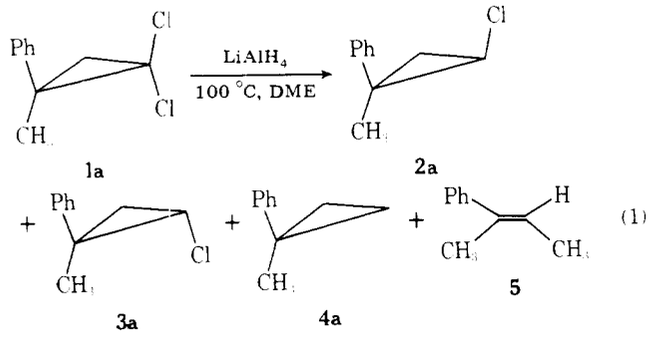
The stereochemistry of reduction of monohalocyclopropanes with $LiAlH_4$ has not been reported. In order to determine the stereochemistry in such a reduction, we have studied the lithium aluminum deuteride ($LiAlD_4$) reduction of an isomeric pair of chlorocyclopropanes, **2a** and **3a.**



2a **3a**

Results

The *gem*-dichlorocyclopropane, **1a,** was prepared by the additon of phase-transfer-generated dichlorocarbene to α-methylstyrene according to the procedure of Makosza.[5] Reduction of **1a** with $LiAlH_4$ in dimethoxyethane (DME) led to a mixture of four products, the percentage of each being dependent on the reaction conditions. Table I lists the product mixtures obtained with varying mole ratios of $LiAlH_4$ to **1a.**[6] Assignments of structure for **2a** and **3a** were made on the basis

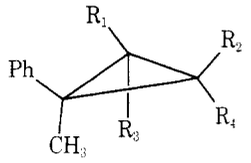


1a **2a** **3a** **4a** **5** (1)

of proton chemical shifts and coupling constants (Table II). Methyl groups are known to shield[7] cis hydrogens on a cyclopropane ring and deshield trans hydrogens with the shielding being greater than the deshielding effect. Using the chemical shift of the protons of cyclopropane (0.22 ppm) as a reference, phenyl[8] and chlorine[9] substituents on a cyclopropane ring deshield adjacent hydrogens. With both substituents, the deshielding of the trans hydrogens is greater than that of the cis. Thus the 0.27-ppm upfield shift of H_3 in **2a** relative to H_1 in **3a** is mainly due to the shielding effect of the methyl cis to H_3 in **2a.** The 0.29-ppm downfield shift seen for H_2 in **3a** relative to H_2 in **2a** is due to the greater trans deshielding effect of chlorine. Finally, the 0.19-ppm downfield shift for H_4 in **2a** relative to H_4 in **3a** is also caused by the deshielding nature of the adjacent chlorine substituent.

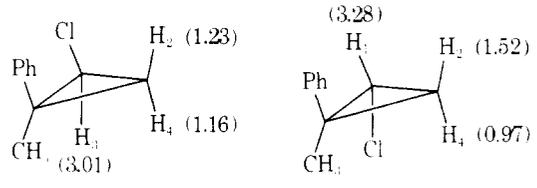
Cyclopropyl chlorides **2a** and **3a** were reduced with lithium aluminum deuteride ($LiAlD_4$), and the stereochemical outcome was determined by ^1H NMR analysis. An authentic

Table II. ^1H NMR Chemical Shifts[a] and Coupling Constants for Substituted Phenylcyclopropanes



compd	CH_3	H_1	H_2	H_3	H_4	Ph
1a, $R_1 = R_3 = Cl$; $R_2 = R_4 = H$	1.63		1.87[b]		1.50[b]	7.17
			$J_{2,4} = 7.0$ Hz			
1b, $R_1 = R_3 = Cl$; $R_2 = H$; $R_3 = D$	1.63		1.87[b]			7.17
2a, $R_1 = Cl$; $R_2 = R_3 = R_4 = H$	1.33		1.23	3.01	1.16	7.17
			$J_{2,3} = 3.6$; $J_{3,4} = 7.6$; $J_{2,4} = -6.7$[c]			
2b, $R_1 = Cl$; $R_4 = D$; $R_2 = R_3 = H$	1.33		1.20	3.00		7.17
			$J_{2,3} = 3.6$			
2c, $R_1 = Cl$; $R_3 = D$; $R_2 = R_4 = H$	1.33					
3a, $R_3 = Cl$; $R_1 = R_2 = R_4 = H$	1.56	3.28	1.52		0.97	7.22
			$J_{1,2} = 7.7$; $J_{1,4} = 4.2$[c]; $J_{2,4} = -6.4$			
4a, $R_1 = R_2 = R_3 = R_4 = H$	1.39		0.82		0.67	7.10
4b, $R_1 = R_2 = R_3 = H$; $R_4 = D$	1.39		0.82		0.67	7.10

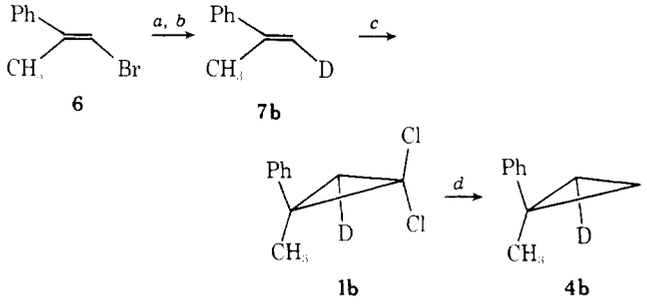
[a] Parts per million (ppm) downfield from tetramethylsilane. [b] These assignments are the reverse of those previously made by M. T. Rodgers (*J. Am. Chem. Soc.*, **84**, 2249 (1962)). [c] The analysis of the spectra was performed using LAOCN 3.[8]



2a **3a**

sample of specifically labeled **4b** was prepared by the stereospecific route illustrated below (Scheme I). The preparation of (*E*)-α-methyl-β-deuteriostyrene (**7b**) from 6 has been reported previously[10] by reaction of **6** with lithium metal in ether solution at −30 °C followed by addition of deuterioacetic acid. A mixture of the *E* and *Z* isomers of **7b** was obtained along with nondeuterated **7.**[11] However, the reaction of **6** with magnesium in THF and a 1.5 molar equiv of ethyl bromide gave greater than 90% stereochemically and isotopically pure **7b** upon treatment with D_2O.[12] The deuterated alkene was transformed into the dichlorocyclopropane[5] and then reduced to the deuterated hydrocarbon (**4b**) with $LiAlH_4$ in DME. The ^1H NMR spectrum of **4b** showed two multiplets for the cyclopropyl hydrogens with the upfield multiplet integrating for one proton (see Figure 2).

Scheme I



6 **7b** **1b** **4b**

[a] Mg/THF, EtBr. [b] D_2O. [c] $CHCl_3$/NaOH/TEBA. [d] $LiAlH_4$/DME, 100 °C, 50 h.

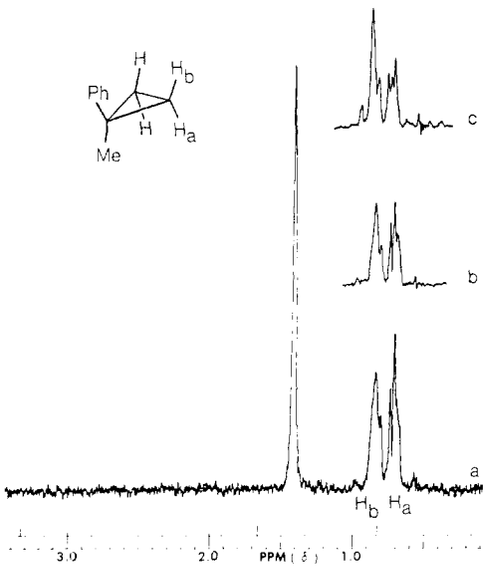
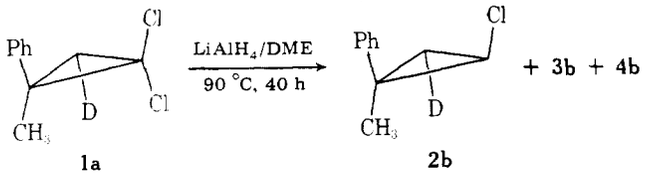


Figure 1. (a) Partial ^{1}H NMR spectrum of **4a;** (b) partial ^{1}H NMR spectrum of **4b** obtained from reduction ($LiAlD_4$) of **2a** with 25% D incorporation; (c) partial ^{1}H NMR spectrum of **4b** obtained from reduction ($LiAlD_4$) of **2a** with greater than 90% D incorporation.

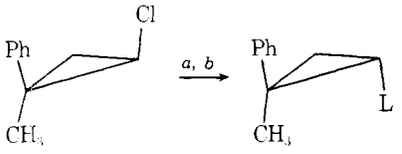
Reduction of **1b** with $LiAlH_4$ in DME under slightly milder conditions (see Experimental Section) led to a mixture of **2b, 4b,** and a minor amount of **3b.** The ^{1}H NMR spectrum of **2b**



1a **2b**

showed an AB pattern with peaks centered at δ 1.2 and 3.0 with a coupling constant of 4.0 Hz, characteristic of trans stereochemistry[8] further confirming the assigned structure for **2a.**

Lithium aluminium deuteride ($LiAlD_4$) reduction of a VPC purified sample of **2a** gave a mixture of **4a** and **4b.** Structural assignment of **4b** was made by comparison of its NMR spectrum with that of an authentic sample. The deuterium content of **4b** was determined by NMR integration. As shown in Figure 1, the cyclopropyl protons of **4a** appear as an AA'BB' set of



4a, L = H
b, L = D

[a] $LiAlD_4$/DME, 110 °C, 166 h. [b] Na_2SO_4/H_2O.

multiplets centered at 0.67 and 0.82 ppm. The upfield multiplet was assigned to the protons cis to methyl. This assignment was based on the known shielding effect of methyl groups on adjacent cyclopropyl protons[7] and on the fact that an authentic sample of the monodeuterio isomer, **4b,** showed a decreased intensity in the upfield multiplet (Figure 2c). This assignment which is internally consistent for the cyclopropyl derivatives prepared in this study (Table II) is opposite to a previous assignment in the literature.[13] The percent deuterium incorporation in **4b** was a function of the amount of solvent used in the reduction (Table III and Figure 1). Within the error of detection (±5%), the reduction (D incorporation) proceeded with complete inversion of configuration. In a similar manner, a VPC purified sample of **3a** was reduced with

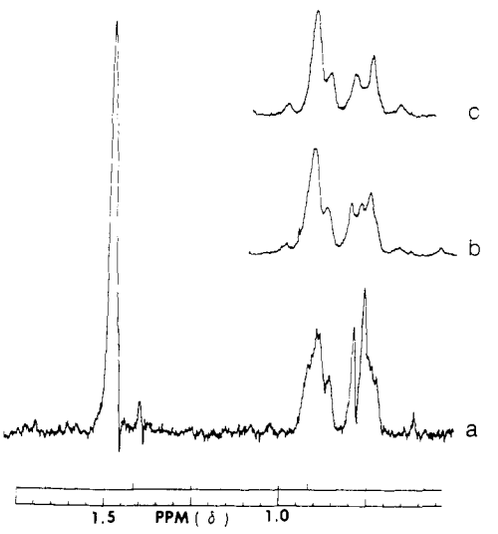
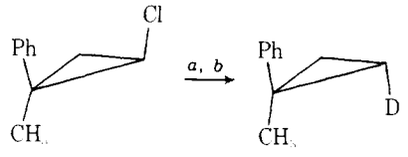


Figure 2. (a) Partial ^{1}H NMR spectrum of **4a;** (b) partial ^{1}H NMR spectrum of **4b** obtained from reduction ($LiAlD_4$) of **3a;** (c) partial ^{1}H NMR spectrum of an authentic sample of **4b.**

Table III. Deuterium Incorporation and Stereochemistry of Reductive Dehalogenation of 2a as a Function of Concentration[a]

mL of DME	molarity of **2a**	% D incorp[b]	stereochem[c]
1	2.0	>90	inversion
5	0.4	40	inversion
10	0.2	25	inversion

[a] In all runs, 350 mg (2 mmol) of **2a** was allowed to react with 440 mg (0.01 mol) of $LiAlD_4$ at 110 °C for 72 h. [b] Determined by NMR integration. [c] Stereochemistry of deuterium incorporated only.



3a **4b**

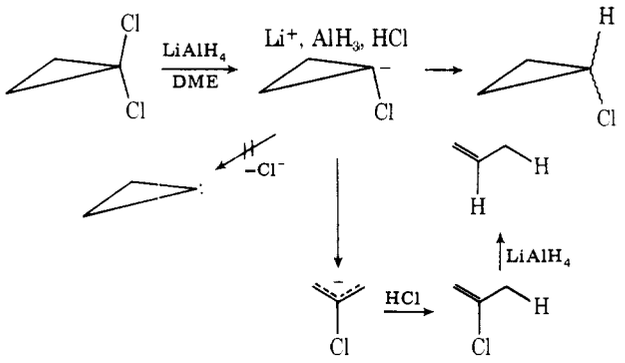
[a] $LiAlD_4$/DME, 110 °C, 166 h. [b] $Na_2SO_4H_2O$.

$LiAlD_4$ to give **4b** (Figure 2). The $LiAlD_4$ reduction of **3a,** therefore, proceeds with complete retention of configuration.

Discussion

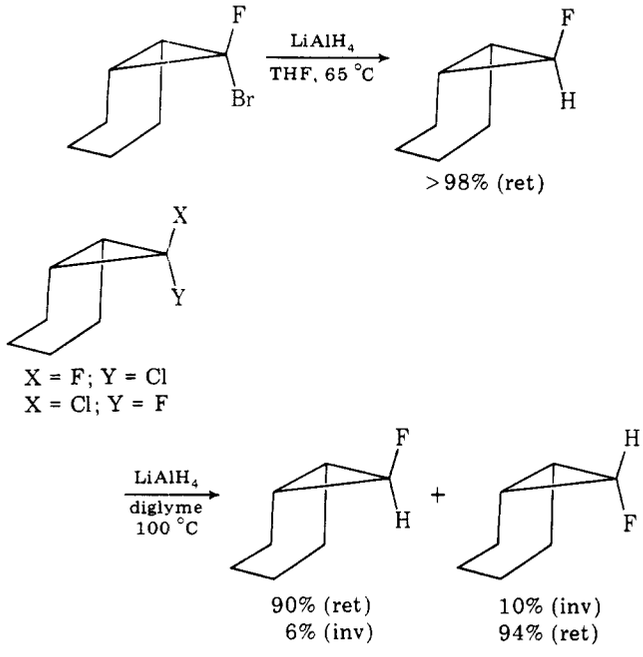
Until recently,[2-4] cyclopropyl halides were thought to be inert toward reduction by lithium aluminium hydride ($LiAlH_4$). The reduction of *gem*-dichlorocyclopropanes[2] with $LiAlH_4$ is known to give monochlorides as well as cyclopropyl hydrocarbons depending on the reaction conditions. A mechanism involving cyclopropyl anions has been proposed by Jefford to account for these results. When the reduction of **1a** was carried out with lithium aluminium deuteride ($LiAlD_4$), complete incorporation (^{1}H NMR) of deuterium occurred at the chlorine-bearing cyclopropyl carbon. Thus, as found by Jefford[4] in the reduction of *gem*-chlorofluorocyclopropanes, an organometallic intermediate did not survive the reduction conditions to be protonated in the aqueous workup. In this study, we also observed alkene formation (eq 1 and Table I) along with the normal reduction products. The alkene may be formed by electrocyclic ring opening of the anion intermediate[14] in competition with the normal reduction pathway (Scheme II). The vinyl chloride initially formed

Scheme II

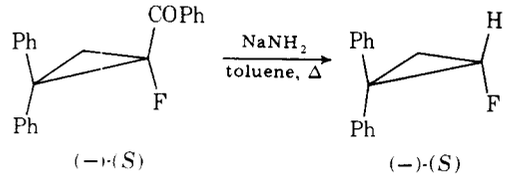


upon ring cleavage would be reduced to the alkene under the reaction conditions used.[15] Products derived from α elimination, namely allenes[16] or bicyclobutanes,[17] were not detected in the product mixture.

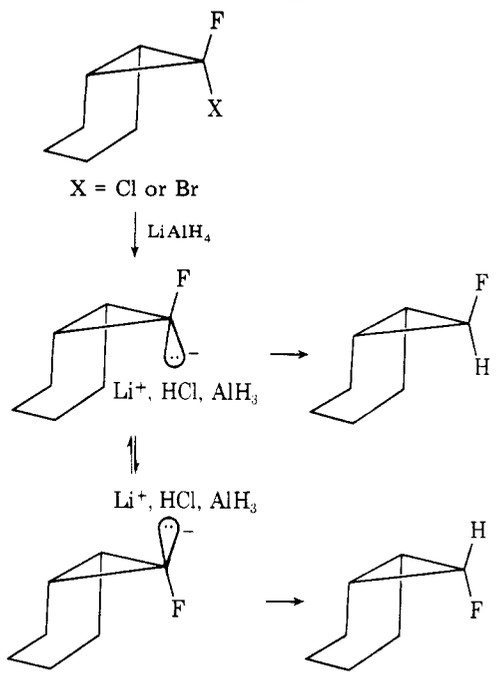
The reduction of *gem*-bromofluorocyclopropanes with $LiAlH_4$ in tetrahydrofuran at 65 °C proceeds stereospecifically with retention of configuration giving monofluorocyclopropanes.[3] Reduction of *gem*-chlorofluorocyclopropanes with $LiAlH_4$ in diglyme at 100 °C proceeds stereoselectively with predominant retention of configuration.[4] The results for the



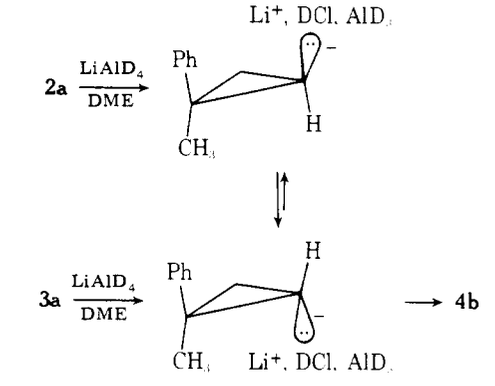
7,7-dihalobicyclo[4.1.0]heptyl system are shown below. A four-center mechanism was originally proposed by Yamanaka[3] to account for the stereospecific reduction of *gem*-bromofluorocyclopropanes. However, both results are consistent with the anion mechanism proposed by Jefford to explain the stereoselective reduction of *gem*-chlorofluorocyclopropanes. Such a mechanism is outlined in Scheme III. Displacement on chlorine or bromine leads to a cyclopropyl anion which captures a proton from the hydrogen halide produced in the initial displacement in competion with anion inversion. In the case of the bromofluoro derivative, the anion produced (THF, 65 °C) is trapped before configurational inversion. However, the same anion produced from the chlorofluoro derivative (diglyme, 100 °C) has sufficient energy to



Scheme III



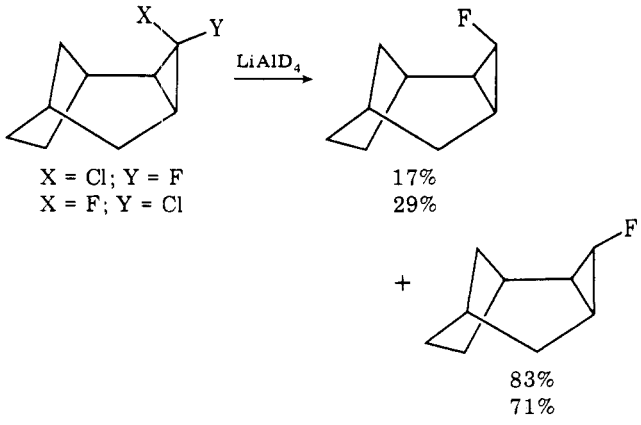
Scheme IV



at least partially equilibrate with its configurational isomer before being trapped. Walborsky has also reported on an α-fluoro-substituted cyclopropyl anion which was able to maintain its configuration when produced in a Haller–Bauer cleavage reaction in refluxing toluene.[18]

The inversion found for the reduction of **2a** and the retention observed for reduction of **3a** is consistent with the anion mechanism shown in Scheme IV. Here the cyclopropyl anion intermediate formed is not α substituted with fluorine and is therefore less stable.[19] However, during its short lifetime, it inverts to an anion configuration which is cis to the β-methyl substituent and trans to the β-phenyl. These results indicate that a cyclopropyl anion produced from the corresponding chloride by $LiAlD_4$ reduction is sufficiently long lived to undergo configurational inversion. In contrast, an α-fluoro-substituted cyclopropyl anion when produced in the same manner has some degree of configurational stability although in the system shown below equilibration is nearly complete.[4] In this tricyclic system as well as in ours, the anion configuration which is preferred has the anion cis or syn to an alkyl group(s). At present, we have no explanation for this preference. Such a preference has also been observed for the α-bromocyclopropyllithium derivative formed on treatment of 7,7-dibromobicyclo[4.1.0]heptane with butyllithium at −95 °C.[20]

Finally, the reduction of monochloride **2a** with $LiAlD_4$ as a relatively dilute solution in DME (Table III) led to incor-



poration of protium, to a large degree, at the site of reduction. Reduction of a mixture of **2a** and **3a** (75:25) with $LiAlH_4$ using deuterium oxide as the quenching reagent produced **4a**, the undeuterated hydrocarbon. Thus in the $LiAlD_4$ reduction the protium incorporation was occurring before the aqueous workup. It is well known that carbanions in general[21] and cyclopropyl anions[22] in particular will abstract a proton from DME forming methyl vinyl ether. The cyclopropyl anion formed from **2a** must be more reactive and therefore less selective than the anion generated from **1a**. Thus, the chlorine-substituted cyclopropyl anion generated from **1a** with $LiAlD_4$ in DME failed to abstract a proton from DME but only formed deuterated monochlorides **2b** and **3b**. A $LiAlH_4$ reduction using DME-d_{10} as solvent gave hydrocarbon product, **4a**, which contained no deuterium. The primary hydrogen isotope effect on the reaction of the anions produced from **2a** and **3a** with DME must be large enough so that the deuterated DME cannot compete with the HCl produced in the reduction as an anion trapping reagent.

Experimental Section

All boiling points are uncorrected. All chemicals were used without further purification, except *n*-pentane which was fractionally distilled and the fraction between 35 and 36 °C collected and 1,2-dimethoxyethane (DME) which was distilled over sodium and benzophenone. Microanalysis was performed by Chemalytics Inc., Tempe, Ariz. Proton magnetic resonance spectra (^1H NMR) were recorded at 60 MHz on a Varian A-60A spectrometer. Chemical shifts are reported in units of δ from internal tetramethylsilane. Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 15 MHz on a JEOL FX-60 spectrometer and are reported in ppm from internal tetramethylsilane. Mass spectra (MS) were obtained with a CEC-21-104 mass spectrometer at an ionization voltage of 70 eV. Gas–liquid phase chromatographic analyses (VPC) and preparative separations were carried out on Hewlett Packard F&M Scientific 700 or 770 gas chromatographs equipped with thermal conductivity detectors.

(*E*)-α-Methyl-β-deuteriostyrene (7b). A mixture of (*E*)-α-methyl-β-bromostyrene[10] (10 g, 0.05 mol), 7.6 g (0.07 mol) of ethyl bromide, and 100 mL of tetrahydrofuran (THF) was added dropwise to a mixture of 3.9 g (0.16 mol) of Mg and 30 mL of THF with stirring over a 3-h period. After completion of the addition, the solution was stirred for 15 min and 3.6 g (0.18 mol) of D_2O was added carefully. The resulting mixture was filtered, and the filtrate was dried ($MgSO_4$) and distilled to give 3.4 g (57%) of **7b**, bp 58–60 °C (10 mm) [(lit.[10] bp 82–85 °C (61 mm)]. The ^1H NMR spectrum showed the alkene to be greater than 90% isomerically pure.

1,1-Dichloro-1-*c*-3-deuterio-*r*-2-methyl-2-phenylcyclopropane (1b). To a mixture of 3.4 g (0.03 mol) of **7b**, 3.5 g (0.03 mol) of $CHCl_3$, and 10 mL of 50% aqueous NaOH was added 0.1 g of benzyltriethylammonium chloride. The mixture was stirred for 48 h, diluted with 50 mL of water, extracted with three 50-mL portions of pentane, and dried ($MgSO_4$). The pentane was removed under reduced pressure and the residue distilled [bp 48–50 °C (0.1 mm)] to give 3.8 g (65%) of **1b**: ^1H NMR (CCl_4) δ 1.63 (s, 3 H), 1.86 (br s, 1 H), 7.18 (s, 5 H). The spectrum showed the isomeric purity to be greater than 90%.

***r*-1-Chloro-*t*-3-deuterio-*t*-2-methyl-2-phenylcyclopropane (2b).** A solution of 4.4 g (0.02 mol) of **1b** in 35 mL of distilled DME and 3.5 g (0.092 mol) of lithium aluminum hydride ($LiAlH_4$) was stirred at 90 °C for 40 h. Saturated sodium sulfate solution was added slowly to the cooled reaction mixture until a white granular precipitate formed. The mixture was filtered, and the precipitate was washed with ether. The resulting filtrate was washed with saturated sodium chloride solution and dried (Na_2SO_4). The solvent was removed at room temperature under reduced pressure, and the residue was distilled to give ca. 1 g (38%) of **4b**, bp 60–64 °C (10 mm), and 0.9 g (26%) of **2b**, bp 38–39 °C (0.25 mm): ^1H NMR (CCl_4) δ 1.2 (d, 1 H, J = 4.0 Hz), 1.33 (s, 3 H), 3.0 (d, 1 H, J = 4.0 Hz), 7.18 (s, 5 H). Analysis by VPC[23] showed this sample to be an 89:11 mixture of **2b** and **3b**, respectively.

1-*c*-2-Deuterio-*r*-1-methyl-1-phenylcyclopropane (4b). In another run, 3.8 g (0.018 mol) of **1b** was reduced with 3.4 g (0.09 mol) of $LiAlH_4$ in DME (35 mL) at 100 °C for 50 h. Workup in the manner described above and distillation gave 2.0 g (84%) of **4b**: bp 65–67 °C (11 mm); ^1H NMR (CCl_4) δ 0.68 (m, 1 H), 0.78 (m, 2 H), 1.39 (s, 2 H), 7.1 (s, 5 H). The ^1H NMR showed the sample to be greater than 90% isomerically pure.

Reduction of 1,1-Dichloro-2-methyl-2-phenylcyclopropane (1a) with $LiAlH_4$. A solution of 10 g (0.049 mol) of **1a** in 50 mL of DME and 9.5 g (0.25 mol) of $LiAlH_4$ was stirred at 100 °C for 72 h. Saturated sodium sulfate solution was added slowly to the cooled reaction mixture until a white granular precipitate was formed. The mixture was filtered, and the precipitate was washed with ether. The combined washings and filtrate were washed with saturated sodium chloride solution, dried (Na_2SO_4), and concentrated in vacuo. The residue upon VPC analysis showed the presence of four components.[23] The components were separated by preparative VPC.[24] The first component (retention time 4.5 min, relative abundance 16.5%) was identical (retention time and ^1H NMR) with an authentic sample of **4a**. The second component (retention time 6.6 min, relative abundance 5.3%) was identical (retention time and ^1H NMR) with an authentic sample of **5**. The third component (retention time 12.9 min, relative abundance 20.0%) was assigned structure **3a** based on spectral analysis (see below). The fourth component (retention time 15.9 min, relative abundance 58.1%) was distilled to give 1.0 g of **2a**: bp 43–44 °C (0.2 mm) as determined by spectral analysis; ^1H NMR (CCl_4) δ 1.16 (d, 1 H, J = 6.7 Hz), 1.23 (d, 1 H, J = 3.6 Hz), 1.33 (s, 3 H), 3.0 (d of d, 1 H, $J_{2,3}$ = 3.6 Hz, $J_{3,4}$ = 7.6 Hz), 7.18 (s, 5 H); mass spectrum (70 eV) *m/e* 166; ^{13}C NMR ($CDCl_3$) δ 140.7 (α, phenyl), 129.1, 127.8, 126.4 (phenyl, o, m, p), 39.0 (methine), 28.0 (quaternary), 27.0 (methyl), 21.9 (methylene).

Anal. Calcd for $C_{10}H_{11}Cl$: C, 72.07; H, 6.61; Cl, 21.29. Found: C, 72.25; H, 6.90; Cl, 21.06.

Reduction of 1,1-Dichloro-2-methyl-2-phenylcyclopropane (1a) with Tri-*n*-butyltin Hydride.[25] A mixture of **1a** (18 g, 8.9 mmol) and 27 g (9.2 mmol) of tri-*n*-butyltin hydride was stirred at 155 °C for 14 h. The mixture was distilled to give 9.2 g (64%) of a mixture of monochlorides **2a** and **3a**, bp 32–80 °C (0.15–0.2 mm). Analysis[23] by VPC showed a 15:85 ratio of **2a**–**3a**. Preparative[24] VPC gave 2.8 g of **3a**, bp 39–40 °C (0.15 mm), as determined by spectral analysis: ^1H NMR (CCl_4) δ 0.97 (d of d, 1 H, $J_{4,2}$ = −6.4 Hz, $J_{4,1}$ = 4.2 Hz), 1.52 (d of d, 1 H $J_{2,4}$ = −6.4 Hz, $J_{2,1}$ = 7.7 Hz), 1.56 (s, 3 H), 3.28 (d of d, 1 H, $J_{1,2}$ = 7.7 Hz, $J_{1,4}$ = 4.2 Hz), 7.22 (s, 5 H; ^{13}C NMR ($CDCl_3$) δ 144.3 (α, phenyl), 128.1, 126.7, 126.1 (phenyl, o, m, p), 40.7 (methine), 26.5 (quaternary), 22.9 (methylene), 21.6 (methyl).

Reduction of *r*-Chloro-*t*-2-methyl-2-phenylcyclopropane (2a) with $LiAlD_4$. A 350-mg (2 mmol) sample of **2a** was allowed to react with 440 mg (10 mmol) of $LiAlD_4$ in DME (10 mL) at 110 °C for 166 h. The reaction was carried out in a 25-mL round-bottom flask equipped with a reflux condenser and a drying tube. The reaction flask was immersed in a oil bath at 110 °C, a temperature which maintained a gentle reflux. Workup in the manner described previously gave a crude sample of **4b**. The crude sample was VPC[24] collected and analysis by ^1H NMR showed 25% deuterium incorporation cis to the methyl group in **4b**. Identical reductions using 5 and 1 mL of DME, run in 10- and 5-mL flasks, respectively, gave samples of **4b** showing 40 and 90% deuterium incorporation, respectively (Figure 1).

Reduction of *r*-1-Chloro-1-*c*-2-methyl-2-phenylcyclopropane (3a) with $LiAlD_4$. A 260-mg (1.55 mmol) sample of **3a** was allowed to react with 330 mg (7.85 mmol) of $LiAlD_4$ in DME (1 mL) at 110 °C for 166 h as described above for **2a**. Workup in the usual manner gave a crude sample of **4b** which was shown by VPC[23] analysis to be pure **4b**. Analysis by ^1H NMR showed greater than 95% deuterium incorporation in the cyclopropane ring in the 2 position cis to the methyl group (Figure 2).

Reduction of a Mixture of 2a and 3a with $LiAlH_4$. A 1-g (6 mmol) sample of monochlorides **2a** and **3a** (75:25), 1.2 g (31.5 mmol) of $LiAlH_4$, and 10 mL of freshly distilled DME were placed in a 25-mL flask. A reflux condenser equipped with a drying tube was attached

to the flask, and the assembly was immersed in an oil bath heated to 100 °C. The slurry was stirred at 100 °C for 48 h and then allowed to cool to room temperature. The reaction was quenched by addition of deuterium oxide (5 mL) and worked up in the usual manner. NMR integration of a VPC[24] collected sample of the product (**4a**) showed no evidence for deuterium incorporation.

Reduction of a Mixture of 2a and 3a with $LiAlH_4$ in DME-d_{10}. A 0.35-g (2.1 mmol) sample of monochlorides **2a** and **3a** (75:25), 0.441 g (11.6 mmol) of $LiAlH_4$, and 5 mL of DME-d_{10} (Merch, Sharp and Dohme Canada) were placed in a 25-mL flask equipped with a reflux condenser and a drying tube. The flask was immersed in an oil bath heated to 100 °C. The slurry was stirred at 100 °C for 50 h, cooled, quenched with water, and worked up in the usual manner. An NMR of the crude product (**4a**) showed no evidence of deuterium incorporation.

Registry No.—**1a**, 3591-42-2; **1b**, 69912-46-5; **2a**, 69912-47-6; **2b**, 69912-48-7; **2c**, 69912-49-8; **3a**, 69912-50-1; **3b**, 69979-97-1; **4a**, 2214-14-4; **4b**, 40474-25-7; **5**, 768-00-3; **6**, 16917-35-4; **7b**, 69912-51-2; chloroform, 67-66-3; lithium aluminum deuteride, 14128-54-2.

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Asymmetric Induction in the Michael Reaction

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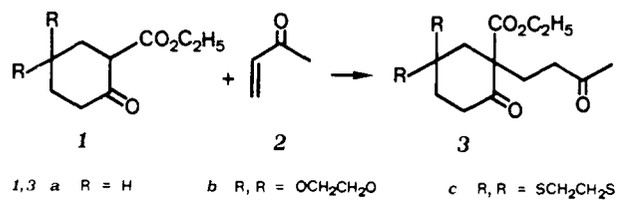
Using cinchona alkaloids (**6, 7**) and derivatives thereof as catalysts in nonpolar solvents, optically active Michael adducts were obtained when cyclohexanone derivates **1a–1c** and the indanone derivative **4** were used as donors and methyl vinyl ketone as the acceptor. The absolute configuration of the adducts was determined. The conversion of the Michael adducts to decalones of type **14a** suggests a synthetic strategy adaptable to the synthesis of chiral terpenes, steroids, and related natural products.

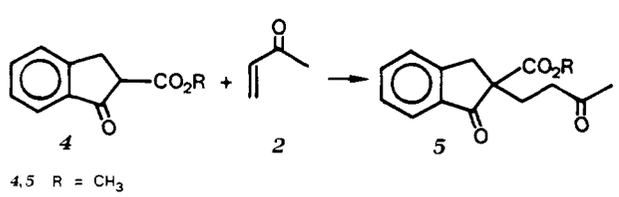
The preparation of optically active compounds by asymmetric induction in C–C bond formation is of primary importance for the synthesis of pharmacologically active compounds such as sesquiterpenes and steroids. Despite considerable efforts in this field, relatively few reactions are known which proceed in reasonable chemical and optical yields.[2-5]

Scheme I



1 2 3

1,3 a R = H b R, R = OCH_2CH_2O c R, R = SCH_2CH_2S



4 2 5

4,5 R = CH_3

The possibility of preparing optically active Michael addition products by use of a chiral basic catalyst was first reported in 1973.[6] In a brief communication from our laboratory, the use of cinchona alkaloids as catalysts in Michael reactions was described (enantiomeric excess up to 71%),[7] while more recently we showed that certain polymer-bound alkaloid derivatives are poor catalysts in reactions of this type.[8]

In the present more systematic study we disclose the results of the alkaloid-catalyzed asymmetric Michael reactions summarized in Scheme I. In addition to testing the influence of variations in the structure of the chiral catalyst, the solvent, and the reaction temperature, we focused our attention on an unambiguous determination of the enantiomeric excess and tried to settle the absolute configuration of the preferentially formed products.

Catalysts. Seven different catalysts were tested. Quinine (**6**), quinidine (**7**), and eucupine (**8**) were from commercial sources, and *O*-acetylquinine (**9**)[9] and quinine methiodide (**10**)[10] were synthesized according to known procedures. Quinine methohydroxide (**11**)[10] and quinidine methohydroxide (**12**)[10] were prepared with the aid of an ion exchange resin from the corresponding iodides and used as about 0.05 or 0.08 M solutions in ethanol (for details, see Experimental Section).

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