Reductions of α-Substituted Ketones by Lithium Diisopropylamide

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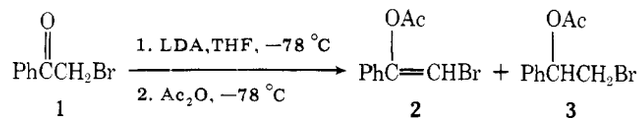
Certain enolizable α-halo- and α-methoxy-substituted ketones undergo rapid reaction with lithium diisopropylamide (LDA) to give reduction products via formal hydride transfer to the carbonyl in competition with enolization. The reducing agent has been verified as LDA by isolation of the oxidized form, the isopropylimine of acetone. This nitrogen analogue of the Meerwein–Ponndorf–Verley reduction gives stereochemistry analogous to that of borohydride or lithium aluminum hydride reductions. From a synthetic standpoint the reduction process can be circumvented in favor of enolization by use of lithium tetramethylpiperidide or lithium hexamethyldisilazide. Reaction of LDA with nonenolizable ketones also leads to reduction, but this process stops short of completion. This has been interpreted in terms of competing nucleophilic addition of LDA to the carbonyl to give an adduct which reverts to starting ketone upon addition of water. Addition of a "ketone scavenger" (methyllithium) to the reaction mixture prior to water quenching does not eliminate the starting ketone. These experiments support the intervention of a 1,2-ketone–LDA adduct.

Lithium diisopropylamide is widely used in synthesis as a hindered, nonnucleophilic base, effecting rapid, kinetically controlled enolization of ketones usually in high yield.[2] During attempts to prepare enolate anions from a variety of enolizable α-halo and α-methoxy ketones by treatment with lithium diisopropylamide (LDA) we have found that, surprisingly, many of these substrates undergo reduction of the carbonyl group in competition with expected enolization. These reactions, over within minutes in ether or tetrahydrofuran (THF) solvent at −78 °C, produce mixtures of reduction and enolization products in which for some ketones the former greatly predominates. Herein we describe the extent of such reduction for several types of ketones with varied α-substituents, the stereochemistry of the reduction, and the interactions of LDA with some nonenolizable ketones as well.

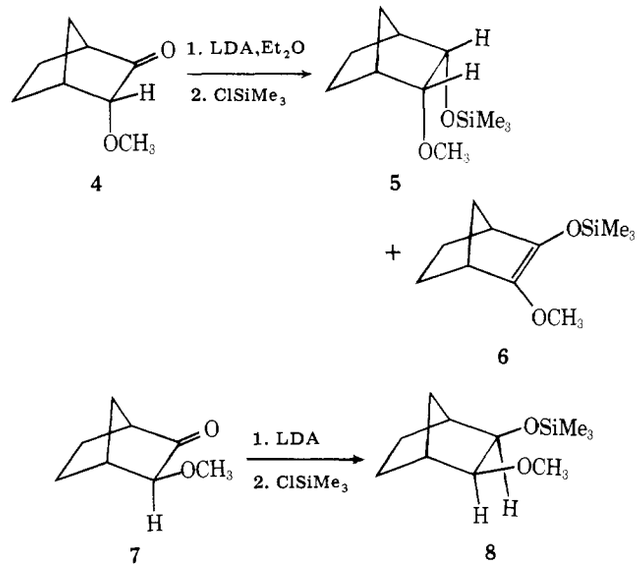
Results and Discussion

Reaction of α-Halo and α-Methoxy Ketones with LDA. We are aware of no reported cases in which LDA has caused reduction of an enolizable ketone;[3] thus we were extremely surprised on examination of the products from the −78 °C reaction of phenacyl bromide **1** with LDA, followed by acetic



anhydride. Obtained in 80% yield was a nearly 2:1 mixture of two products, the minor one of which consisted of the anticipated enol acetate **2** (a single isomer as indicated by the NMR spectrum, but with stereochemistry yet to be determined[4]). The major product proved to be bromo acetate **3**, as shown by spectral comparison with authentic material[5] prepared via acetylation of the sodium borohydride reduction product of **1**. Thus, in the reaction of phenacyl bromide with LDA, reduction of the carbonyl group occurs almost twice as rapidly as ketone enolization.

This type of reaction is not unique to phenacyl bromide. Reaction of LDA with *endo*-3-methoxybicyclo[2.2.1]heptan-2-one, **4**, followed by chlorotrimethylsilane, gave a 71% yield of a 5.6:1 mixture of **5** and **6**. The stereochemistry of **5** was assigned by NMR which showed characteristic coupling (4.3 Hz) of the exo carbinyl protons to the C-1 and C-4 protons. Again carbonyl reduction had occurred at a faster rate than enolization. Reaction of *exo*-3-methoxybicyclo[2.2.1]heptan-2-one, **7**, under the same conditions gave *none* of the product derived from enolization. The sole product was the silated alcohol **8** in which reduction had occurred completely from the endo side of this norbornyl system.



These startling, unprecedented results prompted us to investigate the reaction of LDA with a number of other enolizable α-halo and α-alkoxy ketones. The results of these studies, summarized in Table I, are deserving of several comments. At least seven of the fourteen compounds studied (i.e., **1**, **4**, **7**, **12**, **16**, **34**, and **39**) produced more reduction[6] than enolization with LDA, while only three ketones (**25**, **32**, and **37**) produced no reduction whatsoever. Unfortunately, these compounds exhibit no clear trend which explains why some undergo reduction while others, along with the majority of ketones not bearing α-halo or α-alkoxy substituents, undergo only enolization. What is clear, however, is that for some types of ketones, reduction by LDA is faster than enolization (that LDA is actually the reducing agent has been shown and is discussed below).

Mechanistic and Stereochemical Aspects. The stereochemistry of the reduction products has been carefully determined for those cyclic ketones studied. In all cases the product hydroxyl group is cis to the α-heteroatom. In the cyclohexanone series this stereochemistry is not surprising, for these same cis products predominate in hydride reductions of the corresponding ketones.[7] Since hydride is delivered from the side opposite the heteroatom substituent, however, this implies that complexation of the reducing agent with this substituent is not a prerequisite for reduction. This mode of reduction is preferred even in the reaction of LDA with *exo*-3-methoxybicyclo[2.2.1]heptan-2-one, **7**, and *exo*-3-chlorobicyclo[2.2.1]heptan-2-one, **23**. Hydride is delivered to the

0022-3263/78/1943-2601$01.00/0

Table I

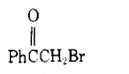
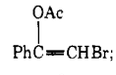
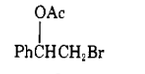
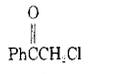
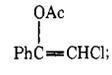
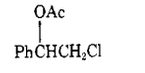
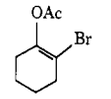
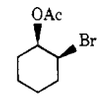
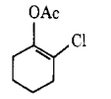
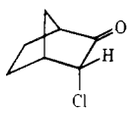
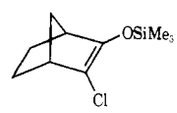
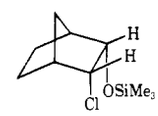
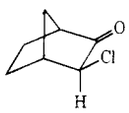
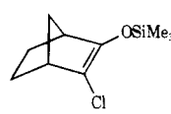
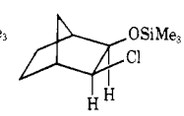
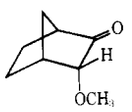
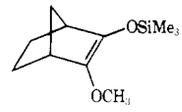
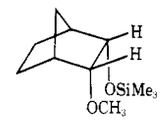
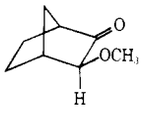
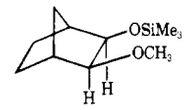
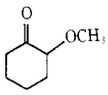
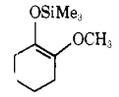
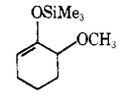
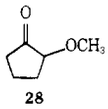
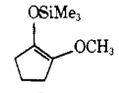
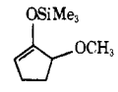
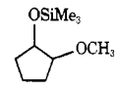
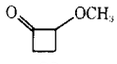
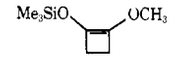
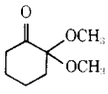
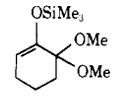
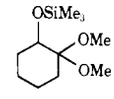
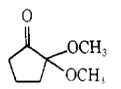
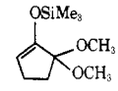
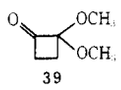
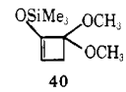
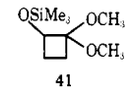
Compound[f]	Base[g]	(No. of equiv)	Solvent	Quenching reagent	Products[h]	Yield[a]	% Reduction[b]	% Enolization[c] toward X
 1	LDA	(1.05)	THF	Ac_2O	 2;  3	80%	63%	
	LHMDS[d]	(1.05)	THF	Ac_2O	**2**	(none)	81%	0%	
 9	LDA	(1.04)	THF	Ac_2O	 10;  11	72%	43%	
	LHMDS	(1.05)	THF	Ac_2O	**10**	(none)	83%	0%	
 12	LDA	(1.11)	THF	Ac_2O	 13;  14;  15	50%	53%	75%
	LHMDS	(1.05)	THF	Ac_2O	**13**	**14**	(none)	75%	0%	82%
 16	LDA	(1.04)	THF	Ac_2O	 17;  18;  19	58%	42%	73%
	LDA	(1.05)	Ether	Ac_2O	**17**	**18**	**19**	68%	72%	80%
	LHMDS	(1.05)	THF	Ac_2O	**17**	**18**	(none)	91%	0%	94%
 20	LDA	(2.2)	Ether	$ClSiMe_3$	 21;  22	90%	17%	
 23	LDA	(2.2)	Ether	$ClSiMe_3$	 21;  24	81%	6%	
	LiTMP[e]		Ether	$ClSiMe_3$	**21**	(none)	92%	0%	
 4	LDA	(1.3)	Ether	$ClSiMe_3$	 6;  5	77%	85%	
	LTMP	(1.5)	Ether	$ClSiMe_3$	**6**	(none)	82%	0%	
 7	LDA	(1.5)	Ether	$ClSiMe_3$	 8	79%	100%	
 25	LDA	(1.5)	Ether	$ClSiMe_3$	 26;  27	80%	0%	15%
 28	LDA	(1.5)	Ether	$ClSiMe_3$	 29;  30;  31	74%	~10%	30%
 32	LDA	(1.9)	Ether	$ClSiMe_3$	 33	20%	0%	100%
 34	LDA	(1.5)	Ether	$ClSiMe_3$	 35;  36	82%	80%	

Table I (*continued*)

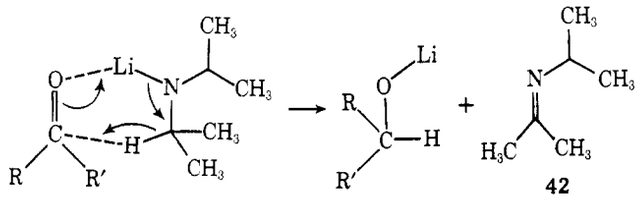
Compound[f]	Base[g]	(No. of equiv)	Solvent	Quenching reagent	Products[h]	Yield[a]	% Reduction[b]	% Enolization[c] toward X
 37	LDA	(2.3)	Ether	$ClSiMe_3$	 38	89%	0%	
 39	LDA	(1.5)	Ether	$ClSiMe_3$	 40  41	40%	72%	

[a] Total yield of purified reduction and enolization products. [b] Percent reduction product in mixture of reduction and enolization products. [c] Percent of enolization product which is enolized toward heteroatom α-substituent. [d] Lithium hexamethyldisilazide. [e] Lithium 2,2,6,6-tetramethylpiperidide. [f] Registry no.: **1**, 70-11-1; **9**, 532-27-4; **12**, 822-85-5; **16**, 822-87-7; **20**, 30860-22-1; **23**, 10464-71-8; **4**, 53329-05-8; **7**, 53329-06-9; **25**, 7429-44-9; **28**, 35394-09-3; **32**, 42083-01-2; **34**, 38461-13-1; **37**, 66057-04-3; **39**, 63703-48-0. [g] Registry no.: LDA, 4111-54-0; LHMDS, 4039-32-1; LiTMP, 38227-87-1. [h] Registry no.: **2**, 66057-05-4; **3**, 5837-69-4; **10**, 66057-06-5; **11**, 829-23-2; **13**, 56974-20-0; **14**, 23029-03-0; **15**, 50421-18-6; **17**, 31151-32-3; **18**, 66057-07-6; **19**, 36375-66-3; **21**, 66057-08-7; **22**, 66057-09-8; **24**, 66057-10-1; **6**, 66057-11-2; **5**, 66057-12-3; **8**, 66057-13-4; **26**, 66057-14-5; **27**, 66057-15-6; **29**, 66057-16-7; **30**, 66057-17-8; **31**, 66057-18-9; **33**, 66057-19-0; **35**, 66057-20-3; **36**, 66057-21-4; **38**, 66057-22-5; **40**, 66057-23-6; **41**, 55057-24-7.

endo side of the bicyclo[2.2.1]heptyl system despite the usually high propensity for exo attack in this system. The same stereochemistry is also seen in the sodium borohydride reduction of **23**.[8]

The LDA reductions also appear to be more stereoselective than mixed hydride reductions. Whereas borohydride reduction of 2-bromocyclohexanone[7a] and lithium aluminum hydride reduction of 2-chlorocyclohexanone[7b] give the cis halo alcohols as major products, appreciable amounts of the trans isomers are also produced. The LDA reactions give exclusively the cis halo alcohols (as acetates). Reaction with *exo*- and *endo*-3-chlorobicyclo[2.2.1]heptan-2-ones, **20** and **23**, also gives exclusively cis alcohols. Additionally we have found that sodium borohydride reduction of *exo*-3-methoxybicyclo[2.2.1]heptan-2-one, **7**, gives a mixture (2.8:1 ratio) of exo and endo alcohols with the exo alcohol predominating. In contrast, the reaction of LDA with **7** gives only the exo silated alcohol **8**. Reasons for the increased stereoselectivity in the reduction of ketones with LDA may lie in the low temperature of the reaction (−78 °C) as well as the steric bulk of the reducing agent.

Considering possible reactions which could account for LDA reductions, one which seems most plausible is a nitrogen analogue of the Meerwein–Ponndorf–Verley reduction, as indicated below. The driving force for such a reaction is the



42

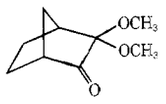
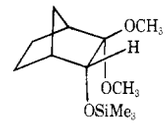
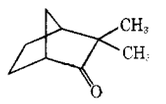
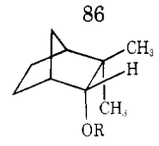
transfer of negative charge from nitrogen to oxygen, and indeed there is precedent for reduction via such a pathway in the reaction of benzophenone with lithium *N*-benzylanilide.[9]

One consequence of this proposed reduction mechanism would be the formation of the oxidized amide reducing agent, that is the isopropylimine of acetone (**42**). In the reaction of phenacyl chloride, **9**, with LDA in THF, a new low boiling compound was indeed formed in large amounts as indicated by gas chromatographic analysis. Separation of a small sample of this material from solvent and residual diisopropylamine by preparative gas chromatography allowed its spectral (NMR) comparison with an authentic sample of **42** prepared via routine methods;[10] the compounds are the same. Diisopropylamine is clearly oxidized in this reaction, strongly suggesting that it serves as the reducing agent for the phenacyl chloride and other ketones.

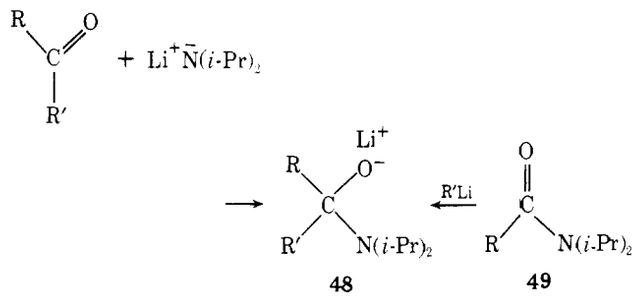
If such a reaction is responsible for the reductions reported in Table I, then amide bases which do not bear hydrogen atoms on the atoms attached to nitrogen should not effect reduction. Indeed, the use of lithium hexamethyldisilazide or lithium 2,2,6,6-tetramethylpiperidide with several compounds which reduce extensively with LDA (**1**, **4**, **9**, **12**, **16**, and **23**) effects no reduction whatsoever. These bases offer a useful alternative to LDA in obtaining enolized product in high yield from "reduction prone" ketones. It is interesting to compare the positions of enolization for several of the ketone structures. Both α-bromo- and α-chlorocyclohexanone enolize largely toward the halogen atom, as expected from the known acidifying effect of these groups.[11] With 2-methoxycyclohexanone, **25**, however, the situation is reversed. Enolization away from the methoxy group heavily predominates (perhaps also to be expected[12]). The trend of increased enolization toward methoxy in **25**, **28**, and **32** is also worth noting. In this case, however, the reasons for the trend are not well understood.

Reaction of LDA with Nonenolizable Ketones. The final phase of this study involved the reaction of LDA with several nonenolizable ketones shown in Table II. Since the enolization pathway is ruled out for all these compounds, it might be expected that reduction would occur as the sole reaction. Indeed, the only products from ketones **43**, **45**, and **47** (runs a, d) are reduction and starting ketone. Oddly enough in no case did reduction reach completion, even with excess LDA. This result can be rationalized in cases when less than 2 equiv of LDA was employed. The by-product imine (**42**) from reductions may well be attacked by LDA itself in a proton abstraction reaction, thus quenching the active amide reducing agent. Such processes have been observed by Wittig in reactions of lithium diethylamide and benzophenone.[9a] With more than 2 equiv of LDA, however, starting material is still recovered, even if the reaction is refluxed for a long period (run **46b**).[9b] This suggests the possibility that perhaps another reaction is competing with reduction, this being 1,2 addition of LDA to the carbonyl. The resulting intermediate **48** is indeed expected to have some stability in aprotic ether or THF solvent, as this is the same intermediate stage at which reaction stops during ketone synthesis from alkyllithium reagents and dialkylamides (e.g. **49** → **48**).[13] Aqueous workup cleaves **48** to produce ketone, which in our case would be starting material.

Table II

Compound[a]	Equiv of LDA	Solvent	Temp, °C	Scavenger	Quenching reagent	Total yield	Products and ratio		
 43	1.5	Ether	−78 to +25	—	$ClSiMe_3$	73%	 44[b] 86	+	St. mat'l. 14
 45							 46		
Run: (a)	1.5	Ether	−78 to +35	—	$ClSiMe_3$	51%	85 (R = $SiMe_3$)[c]		15
(b)	2.2	Ether	−78 to +35	—	H_2O	45%	90 (R = H)[d]		10
Benzophenone (47)							$(Ph)_2\overset{H}{\underset{|}{C}}OH$[e]	St. mat'l.	$(Ph)_2\overset{CH_3}{\underset{|}{C}}OH$[f]
Run: (a)	1.1	THF	−78	—	H_2O	89%	1.2	1	0
(b)	1.1	THF	−78	CH_3Li	H_2O	90%	5	1	4
(c)	0	THF	−78	CH_3Li	H_2O	100%	0	0	100
(d)	4.7	THF	−78	—	H_2O	91%	4.7	1	0
(e)	3.1	THF	−78	CH_3Li	H_2O	61%	5.4	1	0
(f)	3.1	Ether	−78	CH_3Li	H_2O	90%	5.4	1	2.5

[a] Registry no.: **43**, 35611-45-1; **45**, 13211-15-9; benzophenone, 119-61-9. [b] Registry no.: 66057-25-8. [c] Registry no.: 66057-26-9. [d] Registry no.: 640-54-0. [e] Registry no.: 91-01-0. [f] Registry no.: 599-67-7.



48 **49**

To determine whether the recovered starting material from the LDA reductions is present in the reaction mixture as free ketone, or possibly as some nonreactive species such as **48**, a ketone scavenger (methyllithium) was added in excess to the reaction mixture just before workup. Methyllithium certainly reacts rapidly and completely with benzophenone under the reaction conditions (**47c**), and yet ketone was still recovered from all reactions in which methyllithium was added prior to workup (**47b,e,f**). Some species forms in these reactions which is resistant to attack by methyllithium, and yet which regenerates benzophenone on workup. We feel the most reasonable formulation for such a species is adduct **48**.

It can be seen that with 3 equiv of LDA in THF (**47e**), reaction of the ketone was complete (no methyllithium adduct was formed), the ratio of reduction to "regenerated ketone" being about 5:1. When only 1.2 equiv of LDA was used (**47b**), free ketone was indeed present prior to workup and reacted with methyllithium (~40%), but the ratio of reduction to regenerated ketone was still ~5:1. This is the same ratio of reduction to starting material one sees with a large excess of LDA alone (**47d**), and suggests that if adduct **48** is formed, the rate of reduction of benzophenone by LDA is about five times the rate of addition under these conditions.

Conclusions. Our results show that lithium diisopropylamide effects facile reduction of ketones (within minutes at −78 °C), and that this reaction is in many cases competitive with enolization for α-halo and α-alkoxy ketones. It also appears likely that 1,2-addition of LDA to ketones occurs as well, this reaction for benzophenone being only slightly slower than the reduction reaction. In those cases where reduction occurs as an undesired side reaction of ketone enolization by LDA, the problem can be avoided by using lithium tetramethylpiperidide or lithium hexamethyldisilazide as base.

Experimental Section

NMR spectra were recorded on a Varian A-60 A or Varian XL-100 in the Fourier transform mode and are reported in δ (parts per million) relative to tetramethylsilane. Mass spectra were recorded on an AEI Scientific Apparatus MS 902 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer. Dry tetrahydrofuran was distilled from lithium aluminum hydride just before use.

Reactions of α-Halo Ketones with Lithium Hexamethyldisilazide. General Procedure. Lithium hexamethyldisilazide was prepared by adding 1.05 equiv of 2.5 M *n*-butyllithium in hexane to a stirred −78 °C solution of 1.1 equiv of hexamethyldisilazane in 4 mL of dry tetrahydrofuran. To this stirred −78 °C solution was added over a 3-min period a solution of 1.0 equiv (usually 2.0 mmol) of the α-halo ketone in 3 mL of dry tetrahydrofuran. After 11 min, 3 equiv of acetic anhydride was added all at once, and after 30 min longer the cold solution was diluted with 80 mL of ether. This mixture was washed with 25 mL of water, three 25-mL portions of 10% hydrochloric acid, and 25 mL of saturated aqueous sodium chloride, and then dried over magnesium sulfate. After evaporation of the solvent under reduced pressure, the crude material was further treated as described below to obtain the following products.

2-Bromo-1-phenylethenyl Acetate (2). The product from 1 mmol of phenacyl bromide was chromatographed on a 20 × 20 cm silica gel thick layer plate, developed with a 2:1 mixture (by volume) of hexane and methylene chloride. Elution of that UV active band having R_f 0.27 afforded 196 mg (81%) of **2** as a pale yellow liquid: IR (film) 1775, 1630 cm^{-1}; NMR ($CDCl_3$) δ 7.42 (5 H, s), 6.57 (1 H, s), 2.31 (3 H, s); mass spectroscopic molecular weight 241.9790 (calcd for $C_{10}H_9O_2Br$, 241.9767).

2-Chloro-1-phenylethenyl Acetate (10). The product from 1.7 mmol of phenacyl chloride was chromatographed on a 15-g silica gel column. Elution with 5% ethyl acetate in hexane afforded 272 mg (84%) of **10** as a colorless oil: IR (film) 1775, 1630 cm^{-1}; NMR ($CDCl_3$)

δ 7.44 (5 H, s), 6.50 (1 H, s), 2.32 (3 H, s); mass spectroscopic molecular weight 196.0322 (calcd for $C_{10}H_9O_2Cl$, 196.0281).

2-Bromocyclohex-1-enyl Acetate (13) and 6-Bromocyclohex-1-enyl Acetate (14). Gas chromatographic analysis of the crude product obtained from 2.0 mmol of 2-bromocyclohexanone **12** showed peaks for **13** and **14** in a ratio of 82:12 with a small peak (~3% total) corresponding to starting material. Chromatography of this material on a 48-g column of silica gel afforded in order of elution with 5% ethyl acetate in hexane fractions A, B, and C containing a total of 328 mg (75%) of colorless liquid. Fraction A contained 235 mg (54%) of the enol acetate **13**; single peak by gas chromatography: IR (film) 1770, 1680 cm^{-1}; NMR ($CDCl_3$) δ 2.55 (m), 2.19 (s) and 1.76 (m); mass spectroscopic molecular weight 217.9981 (calcd for $C_8H_{11}BrO_2$, 217.9942). As indicated by gas chromatography, fraction B contained a 1:1 mixture of **13** and **14**. Fraction C contained 14 mg (3.2%) of **14**: IR ($CHCl_3$) 1760, 1680 cm^{-1}; NMR ($CDCl_3$) δ 5.66 (1 H, br t, J = 4 Hz), 4.87 (1 H, m), 2.20 (s); mass spectroscopic molecular weight 217.9959 (calcd for $C_8H_{11}BrO_2$, 217.9942).

2-Chlorocyclohex-1-enyl Acetate (17) and 6-Chlorocyclohex-1-enyl Acetate (18). Gas chromatographic analysis of the crude product from 2.0 mmol of 2-chlorocyclohexane **16** showed peaks for **17** and **18** in a ratio of 94:6. Chromatography of this material on a 50-g column of silica gel afforded in order of elution with 1 to 5% ether in hexane fractions A, B, and C containing a total of 282 mg (81%) of colorless liquid. Fraction A contained 193 mg (55%) of the previously reported[14] enol acetate **17**; single peak by gas chromatography: IR (film) 1760, 1680 cm^{-1}; NMR ($CDCl_3$) δ 2.6–2.0 (m), 2.18 (s) and 1.75 (m); mass spectroscopic molecular weight 174.0433 (calcd for $C_8H_{11}ClO_2$, 174.0448). Fraction B contained 83 mg of an 8:1 mixture of **17** and **18** as indicated by gas chromatography. Fraction C contained 6 mg (1.7%) of **18** as an oil; single peak by gas chromatography: IR ($CHCl_3$) 1750 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 5.59 (1 H, t, J = 4 Hz), 4.65 (1 H, m), 2.20 (s); mass spectroscopic molecular weight 174.0466 (calcd for $C_8H_{11}ClO_2$, 174.0448).

Reactions of α-Halo Ketones with Lithium Diisopropylamide in Tetrahydrofuran. General Procedure. Lithium diisopropylamide was prepared by adding 1.04–1.11 equiv of 2.5 M n-butyllithium in hexane to a stirred solution of 1.15 equiv of diisopropylamine in 3 mL of dry tetrahydrofuran at −78 °C. To this stirred −78 °C solution was added over a 4–5-min period a solution of the halo ketone (usually about 2.4 mmol) in 5 mL of dry tetrahydrofuran. After 3 min, 3.1 equiv of acetic anhydride was added, and 1 h later the cold mixture was poured into 80 mL of ether. The mixture was washed with three 25-mL portions of water, one 25-mL portion of ice-cold 10% hydrochloric acid, two 25-mL portions of ice-cold 2% aqueous sodium hydroxide, and one 25-mL portion of saturated aqueous sodium chloride, and then dried over magnesium sulfate. After evaporation of the solvent under reduced pressure, the crude material obtained was further treated as described below.

Reaction of Phenacyl Bromide (1) with LDA. Analysis by gas chromatography and NMR integration of the product obtained from 338 mg of phenacyl bromide (**1**) indicated a 37:63 ratio of 2-bromo-1-phenylethenyl acetate (**2**) to 2-bromo-1-phenylethyl acetate (**3**). Chromatography of this material on an 8-g silica gel column afforded on elution with 20% methylene chloride in hexane an 80% yield of product in three fractions. The first fraction contained 45 mg (11%) of enol acetate **2**; IR and NMR spectra were identical with those of **2** already described above. The second fraction contained a mixture of **2** and **3** as determined by gas chromatography. The final fraction contained 56 mg (14%) of the previously reported[15] acetate **3** as a colorless oil: IR (film) 1745 cm^{-1}; NMR ($CDCl_3$) δ 7.43 (5 H, s), 6.02 (1 H, t, J = 6 Hz), 3.63 (2 H, d, J = 6 Hz), 2.13 (3 H, s). This material was spectrally identical with a sample of **3** prepared via sodium borohydride reduction in ethanol of **1**, followed by acetylation with acetic anhydride in pyridine.

Reaction of Phenacyl Chloride (9) with LDA. Gas chromatographic and NMR analysis of the product from 369 mg (2.4 mmol) of phenacyl chloride **9** indicated a 57:43 ratio of 2-chloro-1-phenylethenyl acetate (**10**) to 2-chloro-1-phenylethyl acetate (**11**). Chromatography of this material on a silica gel column afforded a 72% total yield of product in three fractions. Eluted first was enol acetate **10**; IR and NMR spectra were identical with those of **10** already described above. The middle fraction contained both **10** and **11**. Finally eluted was the previously reported[16] reduction product **11** as a colorless liquid: IR (film) 1745 cm^{-1}; NMR ($CDCl_3$) δ 7.47 (5 H, s), 6.03 (1 H, t, J = 6 Hz), 3.80 (2 H, d, J = 6 Hz) and 2.18 (3 H, s). This material was spectrally identical with a sample of **11** prepared via sodium borohydride reduction in ethanol of **9**, followed by acetylation with acetic anhydride in pyridine.

Reaction of 2-Bromocyclohexanone (12) with LDA. Gas chromatographic and NMR analysis of the product from 667 mg of 2-bromocyclohexanone (**2**) indicated a 35:12:53 ratio of 2-bromocyclohex-1-enyl acetate (**13**) to 6-bromocyclohex-1-enyl acetate (**14**) to *cis*-2-bromocyclohexyl acetate (**15**).

Chromatography of this material on a silica gel column afforded a 50% total yield of product in three fractions. The first and last fractions contained small amounts of pure **13** and **14**, respectively; IR and NMR spectra were identical with those of **13** and **14** already described in a separate procedure above. Upon preparative gas chromatographic separation, the center fraction afforded a pure sample of the previously reported[17] acetate **15**: IR (film) 1745 cm^{-1}; NMR ($CDCl_3$) δ 4.88 (1 H, m), 4.53 (1 H, m), 2.11 (~3 H, s), and 1.2–2.2 (~8 H, m). This material was spectrally identical with a sample of **15** prepared via acetylation of *cis*-2-bromocyclohexanol[7a] by acetic anhydride in pyridine.

Reaction of 2-Chlorocyclohexanone (16) with LDA. Gas chromatographic and NMR analysis of the product from 332 mg (2.5 mmol) of 2-chlorocyclohexanone (**16**) indicated a 45:12:42 ratio of 2-chlorocyclohex-1-enyl acetate (**17**) to 6-chlorocyclohex-1-enyl acetate (**18**) to *cis*-2-chlorocyclohexyl acetate (**19**). Chromatography on a silica gel column afforded a 58% total yield of product in three fractions. The first and last fractions contained small amounts of pure **17** and **18**, respectively, spectrally identical with **17** and **18** prepared in a separate procedure above. Preparative gas chromatographic separation of a small amount of the center fraction afforded the previously reported[7b,17] acetate **19**: IR (film) 1745 cm^{-1}; NMR ($CDCl_3$) δ 5.0 (1 H, m), 4.38 (1 H, m), 2.13, (s). These spectra were identical with those of a sample of **19** prepared via acetylation of *cis*-2-chlorocyclohexanol[7b] by acetic anhydride in pyridine.

Reaction of 2-Chlorocyclohexanone (16) with LDA in Ether. To a stirred solution of 0.31 mL (2.2 mmol) of diisopropylamine in 4 mL of dry ether was added 1.03 mL (2.1 mmol) of 2.05 M methyllithium in ether. After 4 min this solution was cooled with a −78 °C bath and 3 min later a solution of 0.23 mL (2 mmol) of 2-chlorocyclohexanone (**16**) in 3 mL of dry ether was added over a 2-min period. After 14 min, 0.57 mL (6 mmol) of acetic anhydride was added all at once, and 30 min later the mixture was diluted with 80 mL of ether. This mixture was washed with 25 mL of water, two 20-mL portions of 10% hydrochloric acid, and 25 mL of saturated sodium chloride solution, and then dried over magnesium sulfate. The product obtained after removal of solvent under reduced pressure was a 22:6:72 mixture of **17**, **18**, and **19**, respectively, as determined by gas chromatographic and NMR analysis. Chromatography of this material on a 15-g silica gel column afforded in pure form 238 mg (68%) of the same mixture. Characterization of these products has been described above.

Reaction of *exo*-3-Chlorobicyclo[2.2.1]heptan-2-one (23) with LDA. A solution of LDA in ether was prepared from 2.33 g of diisopropylamine and 12.4 mL of 1.84 M methyllithium. After cooling to −78 °C, a solution of 1.50 g of *exo*-3-chlorobicyclo[2.2.1]heptan-2-one **23**[18] in 4 mL of ether was added dropwise over a 10-min period. The mixture was warmed to −50 °C and then recooled to −78 °C. Chlorotrimethylsilane (2.70 g) was added dropwise and the mixture was allowed to warm to room temperature. After 1 h at room temperature an aqueous workup was employed. After drying the organic phase over sodium sulfate, the solvent was removed by distillation through a Vigreux column. The residue was distilled at 14 mm to give 1.81 g (81%) of a mixture of **21** and **24** in a ratio of 94:6 as determined by gas chromatography. Samples of each product were isolated by preparative gas chromatography and identified by NMR spectral comparison with authentic samples prepared as described below. Silyl ether **24** showed the following: NMR ($CDCl_3$) δ (2 H, quartet of doublets, J = 2 Hz, J = 6 Hz), 2.36 (1 H, m), 2.12 (1 H, m), 1.9–1.0 (6 H, m) 0.14 (9 H, s). Silyl ether **24** was identical with a sample prepared by silation of *exo*-3-chlorobicyclo[2.2.1]heptan-*exo*-2-ol with triethylamine and chlorotrimethylsilane.

Reaction of *exo*-2-Chlorobicyclo[2.2.1]heptan-2-one (23) with LiTMP. A solution of LiTMP from 2.08 g of tetramethylpiperidine and 8.0 mL of 1.84 M methyllithium was cooled to −78 °C and a solution of 1.52 g of *exo*-2-chlorobicyclo[2.2.1]heptan-2-one (**23**) in 4 mL of ether was added over a 5-min period. After warming to −50 °C and recooling to −78 °C, 2.0 g of chlorotrimethylsilane was added and the mixture was brought to room temperature. After 1 h at room temperature an aqueous workup followed. The amine was removed by washing the organic phase with a solution of 2.12 g of potassium bisulfate in 20 mL of cold water. After drying over sodium sulfate, the solvent was removed by distillation through a Vigreux column. The residue was distilled to give 2.12 g (92%) of silyl ether **21**, bp 95–97 °C (14 mm); silyl ether **21** showed the following: NMR (CCl_4) δ 2.75 (1 H, m), 2.62 (1 H, m), 1.9–0.9 (6 H, m), 0.22 (9 H, s); mass spectroscopic

molecular weight 216.0736 (calcd for $C_{10}H_{17}ClOSi$, 216.0737).

Methanolysis of 21. A mixture of 1.78 g of **21** and 30 mL of methanol was refluxed for 2.5 h. The solvent was removed by distillation through a Vigreux column and the residue was distilled to give 1.19 (100%) of *endo*-3-chlorobicyclo[2.2.1]heptan-2-one **20**, mp 52–55 °C (lit.[18] mp 55.5–60.5 °C, lit.[19] mp 53–56 °C). Previously reported **20** had the following: NMR (CCl_4) δ 4.07 (1 H, d, J = 4.7 Hz), 3.0–2.5 (2 H, m), 2.2–1.3 (6 H, m).

Reaction of *endo*-3-Chlorobicyclo[2.2.1]heptan-2-one (20) with LDA. The procedure was analogous to that of the exo isomer **23**. LDA from 1.62 g of diisopropylamine and 8.6 mL of 1.84 M methyllithium with 1.04 g of **20** gave 1.41 g (90%) of a 83:17 mixture of **21** and **22**. Samples of each product were isolated by preparative gas chromatography. The major product was identical with the product produced in reaction of **23** with LiTMP. The minor product, silyl ether **22**, showed the following: NMR ($CDCl_3$) δ 4.06 (2 H, AB quartet of doublets, J = 4.0 Hz, J = 8.8 Hz), 2.43 (1 H, m), 2.25 (1 H, m) 2.1–1.0 (6 H, m), 0.12 (9 H, s). The stereochemistry of **22** was assigned based on the magnitude (4.0 Hz) of the coupling in the AB pattern.

Reactions of Methoxy Ketones with Lithium Diisopropylamide. General Procedure. Methyllithium (1.3–2.3 equiv) was added dropwise under nitrogen to a 5 to 10% excess of diisopropylamine dissolved in an equal volume of anhydrous ether. The solution was then cooled to −78 °C. One equivalent of the ketone was dissolved in anhydrous ether and was added slowly dropwise to the −78 °C solution. After the addition was completed, the reaction was warmed slowly to −20–0 °C and recooled immediately to −78 °C. Chlorotrimethylsilane (molar equivalent of the diisopropylamine used) was added all at once and the cold bath was removed. After stirring at room temperature for 30 to 45 min, water was added. The phases were separated and the organic layer was extracted with cold water and saturated sodium chloride solution, and dried (sodium sulfate). The solvents were removed by distillation through a Vigreux column on a steam bath or by rotary evaporator and the residue was distilled.

Reaction of 2-Methoxycyclohexanone (25) with LDA. Diisopropylamine (0.75 g), 3.82 mL of 1.84 M methyllithium, and 0.60 g of **25**[20] gave 0.75 g of products: bp 56–65 °C (1.7 mm). The major product (~85% of the mixture) was 1-trimethylsiloxy-6-methoxycyclohexene (**27**): IR (neat) $\nu_{C=C}$ 5.98 μm; NMR (CCl_4) δ 4.7–4.9 (1 H, m), 3.2–3.5 (4 H, m with sharp s at 3.30), 0.9–2.2 (6 H, m), 0.13 (9 H, s); mass spectroscopic molecular weight 200.1234 (calcd for $C_{10}H_{20}O_2Si$, 200.1233). A signal at δ 3.42 was tentatively assigned as the methoxy signal in **26**.

Reaction of 2-Methoxycyclopentanone (28) with LDA. Diisopropylamine (0.93 g), 4.8 mL of 1.84 M methyllithium, and 0.70 g of **28**[20] gave 0.84 g (74%) of a mixture of three products: bp 76–84 °C (12 mm). The major product (65% of mixture) was 1-trimethylsiloxy-5-methoxycyclopentene (**30**): IR (neat) $\nu_{C=C}$ 6.05 μm; NMR (CCl_4) δ 4.6–4.8 (1 H, m), 3.8–4.1 (1 H, m), 3.22 (3 H, s), 1.4–2.5 (4 H, m), 0.13 (9 H, s). 1-Methoxy-2-trimethylsiloxycyclopentene (**29**) (27% of the mixture) showed: IR (neat) $\nu_{C=C}$ 5.86 μm; NMR (CCl_4) δ 3.50 (3 H, s), 1.4–2.4 (6 H, m), 0.08 (9 H, m). Presence of the reduction product 1-methoxy-2-trimethylsiloxycyclopentane (~10%) **31** was inferred from methanolysis of the product mixture as described below.

Reaction of 2-Methoxycyclobutanone (32) with LDA. Diisopropylamine (1.1 g), 5.64 mL of 1.84 M methyllithium, and 0.54 g of **32**[20] gave 0.19 g (20%) of 1-methoxy-2-trimethylsiloxycyclobutene **33** containing two minor impurities: bp 45–60 °C (25–30 mm); IR (neat) $\nu_{C=C}$ 5.80 μm; NMR (CCl_4) δ 3.59 (3 H, s), 2.07 (4 H, s), 0.14 (9 H, s).

Reaction of *endo*-3-Methoxybicyclo[2.2.1]heptan-2-one (4) with LDA. Diisopropylamine (0.58 g), 3.0 mL of 1.84 M methyllithium, and 0.60 g of **4**[20] gave 0.70 g (77%) of a mixture of **5** and **6**: bp 65–68 °C (1.5 mm). The product ratio was 5.7:1 as determined by NMR. The enol ether **6** was identical with that prepared below. The silyl ether **5** showed: NMR (CCl_4) δ 3.87 (1 H, d of d, J = 9 Hz and 4.3 Hz), 3.1–3.4 (4 H, m with sharp s at 3.21), 0.9–2.4 (8 H, m), 0.05 (9 H, s).

Reaction of 2,2-Dimethoxycyclohexanone (34) with LDA. Diisopropylamine (0.80 g), 4.1 mL of 1.84 M methyllithium, and 0.80 g of **34** (prepared as described below) gave 0.96 g (82%) of a 4:1 mixture of 1,1-dimethoxy-2-trimethylsiloxycyclohexane **36** and 6,6-dimethoxy-1-trimethylsiloxycyclohex-1-ene **35**. Enol ether **35** showed the following: NMR (CCl_4) δ 4.7–5.0 (1 H, m), 3.18 (6 H, s), 0.9–2.2 (6 H, m), 0.09 (9 H, s). Ether **36** showed the following: NMR (CCl_4) δ 3.7–3.9 (1 H, m), 3.09 (6 H, s), 0.9–2.2 (6 H, m), 0.05 (9 H, s).

Reaction of 2,2-Dimethoxycyclopentanone (37) with LDA. Diisopropylamine (0.35 g), 1.8 mL of 1.84 M methyllithium, and 0.21 g of **37** (prepared as described below) gave 0.28 g (89%) of 1-trimethylsiloxy-5,5-dimethoxycyclopent-1-ene **38**: bp 76–84 °C (6–8 mm); IR (neat) $\nu_{C=C}$ 6.03 μm; NMR (CCl_4) δ 4.65–4.85 (1 H, m), 3.20 (6 H, s), 1.5–2.4 (4 H, m), 0.15 (9 H, s). Enol ether **38** lost methanol upon preparative gas chromatography to give 1-trimethylsiloxy-4-methoxycyclopentadiene: IR (neat) $\nu_{C=C}$ 6.13 and 6.34 μm; NMR (CCl_4) δ 5.14 (1 H, q, J = 2.3 Hz, further coupled with J less than 1 Hz) 4.93 (1 H, q, J = 2.3 Hz, further coupled with J less than 1 Hz), 3.64 (3 H, s), 2.62 (1 H, t, J = 2.3 Hz, further coupled with J less than 1 Hz), 0.17 (9 H, s); mass spectroscopic molecular weight 184.0924 (calcd for $C_9H_{16}O_2Si$, 184.0920).

Reaction of 2,2-Dimethoxycyclobutanone (39) with LDA. Diisopropylamine (0.40 g), 1.88 mL of 1.84 M methyllithium, and 0.26 g of **39**[20] gave 0.23 g of a product mixture containing **40** and **41** and unidentified products. Approximately 70% of the product mixture consisted of **40** and **41** which were separated from other products by preparative gas chromatography. Enol ether **40** had the following properties: IR (neat) $\nu_{C=C}$ 6.13 μm; NMR (CCl_4) δ 4.75–4.85 (1 H, m), 3.27 (6 H, s), 2.0–2.2 (2 H, m), 0.20 (9 H, s). Ether **41** had the following properties: NMR (CCl_4) δ 3.9–4.3 (1 H, m), 3.24 (3 H, s), 3.10 (3 H, s), 1.3–2.2 (4 H, m), 0.08 (9 H, s). The products **40** and **41** were present in a 1 to 2.5 ratio.

Reaction of *exo*-3-Methoxybicyclo[2.2.1]heptan-2-one (7) with LDA. Diisopropylamine (0.46 g), 2.3 mL of 1.84 M methyllithium, and 0.40 g of **7**[20] gave 0.48 g (79%) of **8**: bp 65–75 °C (2.0 mm); NMR (CCl_4) δ 3.65 (1 H, d of d, J = 6 Hz and 1.5 Hz), 3.25 (3 H, s), 2.99 (1 H, d of d, J = 6 Hz and 1.5 Hz), 0.7–2.3 (8 H, m), 0.05 (9 H, s); mass spectroscopic molecular weight 214.1407 (calcd for $C_{11}H_{22}O_2Si$, 214.1389).

Reaction of 3,3-Dimethoxybicyclo[2.2.1]heptan-2-one (43) with LDA. Diisopropylamine (0.30 g), 1.45 mL of 1.84 M methyllithium, and 0.30 g of **43**[21] gave 0.37 g of a mixture of unreacted **43**, **44**, and hydrolyzed **44**. Material balance was 73% with the reduction product to starting material ratio of 86:14. Ether **44** had the following properties: NMR (CCl_4) δ 3.68 (1 H, d, J = 4.5 Hz), 3.15 (3 H, s), 3.07 (3 H, s), 2.0–2.4 (2 H, m), 0.9–2.0 (6 H, m), 0.08 (9 H, s); mass spectroscopic molecular weight 244.1491 (calcd for $C_{12}H_{24}O_2Si$, 244.1495).

Methanolysis of Silyl Ethers. General Procedure. The products from reaction of the methoxy ketones with LDA and chlorotrimethylsilane were dissolved in methanol (100 mg of product/mL of methanol) containing a trace of sodium methoxide. The methanolysis was monitored by gas chromatography. When the reactions were completed, the solvent was removed and the products were distilled or collected by preparative gas chromatography and spectra were compared to those of authentic samples.

Methanolysis of 27. Methanolysis of **1a** gave **25** contaminated with trace amounts of another unidentified compound.

Methanolysis of 29, 30, and 31. Methanolysis of the products of reaction of **28** with LDA gave two compounds in a ratio of 9:1. The major product was **28**. The minor product was identified as *cis*-2-methoxycyclopentanol which was independently synthesized as described below.

Methanolysis of 33. Methanolysis of **33** gave 1,1,2-trimethoxycyclobutane. Apparently **32** was ketalized under the reaction conditions.

Methanolysis of 5 and 6. Products from the reaction of **4** with LDA, upon methanolysis, gave a 1:5 mixture of **4** and *endo,cis*-2-methoxy-3-hydroxybicyclo[2.2.1]heptane. The major product was identical with that obtained by borohydride reduction of **4** as described below.

Methanolysis of 35 and 36. Methanolysis of the products of reaction of **34** with LDA gave 2,2-dimethoxycyclohexanol and **34** in a 4:1 ratio.

Methanolysis of 38. Enol ether **38** was methanolyzed to give **37** as the only product.

Methanolysis of 40 and 41. The products from reaction of **39** with LDA, upon methanolysis, gave a 2.1:1 ratio of 2,2-dimethoxycyclobutanol and **39**.

Reduction of Methoxy Ketones with Sodium Borohydride. General Procedure. The ketone was added to a suspension of sodium borohydride in methanol in a cold water bath. Stirring at room temperature was continued for 1 to 2 h and dilute acetic acid was added. The aqueous phase was extracted with ether. The ether phase was extracted with water, dilute sodium carbonate, and saturated sodium chloride, and dried (sodium sulfate). The solvent was removed by distillation through a Vigreux column and the products were distilled.

Reduction of 4. Ketone **4** (0.20 g), 0.05 g of sodium borohydride gave 0.14 g (69%) of endo alcohol: bp 56–58 °C (1.7 mm); IR (neat) ν_{OH}

2.76 μm; NMR (CCl_4) δ 3.79 (1 H, d of d, J = 4 Hz and 9 Hz), 3.1–3.5 (4 H, m with sharp s at 3.34), 2.83 (1 H, s, exchanges with D_2O), 2.1–2.5 (2 H, m), 1.0–2.0 (6 H, m); mass spectroscopic molecular weight 142.1007 (calcd for $C_8H_{14}O_2$, 142.0994). The product was identical with the product of methanolysis of **5**.

Reduction of 7. Ketone **7** (0.24 g) and 0.05 g of sodium borohydride gave 0.17 g (71%) of a 2.8:1 mixture of exo and endo alcohols: bp 60–65 °C (2.0 mm). The exo alcohol had the following characteristics: IR (neat) ν_{O-H} 2.72 μm; NMR ($CDCl_3$) δ 3.68 (1 H, d of d, J = 7 Hz and 2 Hz), 3.42 (3 H, s), 3.1–3.3 (2 H, m, one H exchanged with D_2O and revealed a d of d at 3.23 with J = 7 Hz and 2 Hz), 2.1–2.4 (2 H, m), 0.9–1.9 (6 H, m); mass spectroscopic molecular weight 142.1014 (calcd for $C_8H_{14}O_2$, 142.0994). The alcohol was identical with the product of methanolysis of **8**. The endo alcohol had the following characteristics: IR (in CCl_4) ν_{O-H} 2.79 μm; NMR ($CDCl_3$) δ 3.8–4.0 (1 H, m), 3.33 (3 H, s), 2.85–2.95 (1 H, m), 2.2–2.4 (2 H, m), 0.9–1.9 (6 H, m); mass spectroscopic molecular weight 142.0977 (calcd for $C_8H_{14}O_2$, 142.0994).

Preparation of *cis*-2-Methoxycyclopentanol. *cis*-1,2-Cyclopentanediol[23] (0.68 g) was added to a suspension of 0.18 g of sodium hydride in 3 mL of THF. The mixture was heated to reflux and cooled. Methyl iodide (0.95 g) was added and refluxing was continued for 45 min. Water and ether were added and the phases were separated. The ether layer was extracted with water and saturated sodium chloride, and dried (sodium sulfate). Solvents were removed and the residue was distilled to give 0.31 g of a mixture of mono- and dimethylated diol in about a 1:1 ratio: bp 57–68 °C (15 mm). For the *cis*-methoxy alcohol, the following properties were observed: NMR (CCl_4) δ 3.8–4.2 (1 H, m), 3.3–3.7 (4 H, m with sharp s at 3.33), 2.0–2.3 (1 H, m, exchanges with D_2O), 1.4–2.0 (6 H, m); mass spectroscopic molecular weight 116.0837 (calcd for $C_6H_{12}O_2$, 116.0836). This product was identical with the minor product of methanolysis of the LDA reaction products of **28**.

Preparation of 2-Methoxy-3-trimethylsiloxybicyclo[2.2.1]-hept-2-ene (6). The procedure was the same as that used for the preparation of **21**. Tetramethylpiperidine (4.54 g), 17 mL of 1.84 M methyllithium, 3 g of **4**, and 3.67 g of chlorotrimethylsilane gave 3.74 g (82%) of **6**: bp 65–75 °C (1.7 mm); IR (neat) $\nu_{C=C}$ 5.95 μm; NMR (CCl_4) δ 3.56 (3 H, s), 2.6–2.8 (1 H, m), 2.4–2.6 (1 H, m), 0.7–1.9 (6 H, m) 0.13 (9 H, s); mass spectroscopic molecular weight 212.1238 (calcd for $C_{11}H_{20}O_2Si$, 212.1233).

Preparation of 37. The Swern[23] oxidation procedure was employed. Dimethyl sulfoxide (2.2 mL) was dissolved in 18 mL of methylene chloride and the solution was cooled to −65 °C in a dry ice–acetone bath. Trifluoroacetic anhydride (3.13 g) was added dropwise slowly and stirring was continued for 10 min. 2,2-Dimethoxycyclopentanol[20] (1.28 g), dissolved in 1.5 mL of dimethyl sulfoxide and 15 mL of methylene chloride, was slowly added dropwise. After stirring for 20 min, 3.62 g of trimethylamine was added and the cold bath was removed. Stirring was continued for 15 min at room temperature. Workup consisted of dilution with ether and extraction with several portions of water and saturated sodium chloride, and drying over sodium sulfate. Solvents were removed through a Vigreux column and the residue was distilled to give 1.06 g (84%) of **6**: bp 78–84 °C (12 mm); IR (neat) $\nu_{C=O}$ 5.68 μm; NMR (CCl_4) δ 3.23 (6 H, s), 1.6–2.4 (6 H, m); mass spectroscopic molecular weight 144.0784 (calcd for $C_7H_{12}O_3$, 144.0786).

Preparation of 34. The procedure was identical with that used in the preparation of **37**. Dimethyl sulfoxide (1.33 mL), 11 mL of methylene chloride, 1.97 g of trifluoroacetic anhydride, 1 g of 2,2-dimethoxycyclohexanol[20] (dissolved in 1 mL OF Me_2SO and 2 mL of methylene chloride), and 2.0 g of triethylamine gave 0.89 g (90%) of **5**: bp 66–69 °C (2.1 mm); IR (neat) $\nu_{C=O}$ 5.77 μm; NMR (CCl_4) δ 3.22 (6 H, s), 2.3–2.6 (2 H, m), 1.5–2.1 (6 H, m); mass spectroscopic molecular weight 158.0876 (calcd for $C_8H_{14}O_3$, 158.0943).

Reaction of 3,3-Dimethylbicyclo[2.2.1]heptan-2-one (45) with LDA. Reaction of 1.00 g of camphenilone **45** with LDA from 1.62 g of diisopropylamine and 8.7 mL of 1.84 M methyllithium gave, after quenching with water and an aqueous workup, 0.45 g (45%) of a mixture of 3,3-dimethylbicyclo[2.2.1]heptan-*endo*-2-ol **46** (R=H) and unreacted camphenilone (**45**) in a ratio of 9:1 as determined by gas chromatography.

Isopropylideneisopropylamine (42). To a stirred, −78°C solution of 0.31 mL (2.21 mmol) of diisopropylamine in 4 mL of dry tetrahydrofuran was added 0.73 mL (2.11 mmol) of 2.9 M butyllithium in hexane. Analysis of aliquots from this mixture by gas chromatography showed a large peak of identical retention time to diisopropylamine and no peak corresponding to imine **42**.[10] To the −78 °C solution was then added a solution of 311 mg (2.01 mmol) of phenacyl chloride (**9**) in 3 mL of dry tetrahydrofuran. After 5 min the pressure in the system was cautiously reduced and the cooling bath was removed. The volatiles distilled into a trap cooled at −78 °C. Essentially all of the liquid distilled below room temperature. The reaction flask was approximately 0 °C when the distillation was stopped. Analysis of the distillate by gas chromatography now indicated about a 1:2 ratio of a new peak, corresponding in retention time to authentic imine **42**, and diisopropylamine. Isolation of a sample of the smaller peak by preparative gas chromatography afforded a sample for NMR analysis. The NMR spectrum corresponds to that of imine **42** prepared from isopropylamine and acetone:[10] NMR ($CDCl_3$) δ 3.63 (1 H, sept, J = 6.5 Hz), 1.94 (3 H, s), 1.84 (3 H, s), and 1.11 (6 H, d, J = 6.5 Hz). The spectrum also shows a trace of THF.

Reactions of Benzophenone (47) with LDA. Run (a). To a stirred −78 °C solution of 0.169 mL (1.2 mmol) of diisopropylamine in 3 mL of dry tetrahydrofuran was added 0.46 mL (1.1 mmol) of 2.4 M *n*-butyllithium in hexane. After 3 min a solution of 182 mg (1 mmol) of benzophenone in 3 mL of dry tetrahydrofuran was added dropwise over a 3-min period, causing a lime green color to appear. After 13 min, the −78 °C solution was poured into 80 mL of ether, washed with 20 mL of water, 20 mL of 10% hydrochloric acid, and 20 mL of saturated aqueous sodium chloride, and then dried over magnesium sulfate. After removal of the solvent, the resulting product was chromatographed on a 20 × 20 cm silica gel thick layer plate, developed with 18% ether in hexane. Obtained were 74 mg (40%) of benzophenone (R_f 0.36) and 89 mg (49%) of benzhydrol (R_f 0.17); products were spectrally identical with commercially available materials.

Run (b). The same amounts and reaction conditions were employed as in run (a) except that 9 min after addition of the benzophenone solution, 1.07 mL (2.2 mmol) of 2.05 M methyllithium in ether was added. The solution was then allowed to warm slowly to −50 °C over a 1-h period, before being worked up as above. There was obtained 169 mg (90%) of a 5:1:4 mixture of benzhydrol, benzophenone, and 1,1-diphenylethanol as indicated by IR and NMR analysis.

Run (d). To a stirred −78 °C solution of 0.308 mL (2.2 mmol) of diisopropylamine in 3 mL of dry tetrahydrofuran was added 0.875 mL (2.1 mmol) of 2.4 M *n*-butyllithium in hexane. After 3 min a solution of 82 mg (0.45 mmol) of benzophenone in 3 mL of dry tetrahydrofuran was added dropwise over a 5 min period. After 13 min, the reaction mixture was worked up, chromatographed, and analyzed as in run (a) to afford 13 mg (16%) of benzophenone and 62 mg (75%) of benzhydrol.

Run (e). To a stirred −78 °C solution of 0.45 mL (3.3 mmol) of diisopropylamine in 3 mL of dry tetrahydrofuran was added 1.07 mL (3.1 mmol) of 2.19 M *n*-butyllithium in hexane. After 3 min, a solution of 182 mg (1 mmol) of benzophenone in 3 mL of dry tetrahydrofuran was added over a 3-min period. After 13 min, 2.05 mL (4.2 mmol) of 2.05 M methyllithium in ether was added to the green −78 °C solution, and 2 min later the reaction mixture was worked up, chromatographed, and analyzed as in run (a) to afford 17 mg (9%) of benzophenone and 92 mg (50%) of benzhydrol. No 1,1-diphenylethanol could be detected in the crude product by NMR analysis.

Run (f). To a stirred room temperature solution of 0.45 mL (3.3 mmol) of diisopropylamine in 3 mL of dry ether was added 1.51 mL (3.1 mmol) of 2.05 M methyllithium in ether. The solution was cooled in a −78 °C bath, and a solution of 182 mg (1 mmol) of benzophenone in 3 mL of ether was added over a 3-min period. During the addition a blood red color formed, which gradually faded after 5 min. After another 11 min, 2.05 mL (4.2 mmol) of 2.05 M methyllithium in ether was added, and 2 min later the mixture was worked up as in run (a) to afford 168 mg (90%) of a 5.4:1:2.5 mixture of benzhydrol, benzophenone, and 1,1-diphenylethanol as determined by IR and NMR analysis.

Addition of Methyllithium to Benzophenone. Run (c). To a stirred −78 °C solution of 182 mg (1 mmol) of benzophenone in a mixture of 6 mL of dry tetrahydrofuran and 0.38 mL of hexane was added 1.07 mL (2.2 mool) of 2.05 M methyllithium in ether. After 1 min, the −78 °C solution was poured into a mixture of 80 mL of ether and 20 mL of water, and the ether layer was then washed with 25 mL of 10% hydrochloric acid and 25 mL of saturated aqueous sodium chloride solution. Drying the solution over magnesium sulfate and removal of solvent under reduced pressure afforded 198 mg (100%) of crude 1,1-diphenylethanol. No benzophenone could be detected in this product, either by IR or TLC analysis.

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Registry No.—**42,** 3332-08-9; hexamethyldisilazane, 999-97-3; diisopropylamine, 108-18-9; 1-trimethylsiloxy-4-methoxycyclopentadiene, 66057-27-0; *endo,cis*-2-methoxy-3-hydroxybicyclo[2.2.1]heptane, 53329-03-6; *exo,cis*-2-methoxy-3-hydroxybicyclo[2.2.1]heptane, 53329-04-7; *cis*-1,2-cyclopentanediol, 5057-98-7; *cis*-2-methoxycyclopentanol, 13051-91-7; tetramethylpiperidine, 768-66-1; 2,2-dimethoxycyclopentanol, 63703-33-3; 2,2-dimethoxycyclohexanol, 63703-34-4.

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(24) **Note Added in Proof.** We have found that even cyclohexanone, when treated with LDA as described for **4,** affords 34% reduction. The ratio of reduction to enolization appears sensitive to both solvent (more reduction in ether than in THF) and to the nature of the commercial alkyllithium reagent used to prepare the LDA (more reduction with methyllithium containing lithium bromide than when prepared from *n*-butyllithium).

Hydride Transfer Reduction–Rearrangement of 4-Homobrendylcarbinols. Concomitant Ring Enlargement and Skeletal Isomerization in a Tricyclic 2-Norbornylcarbinyl System

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By the brief contact with 95% sulfuric acid and *n*-pentane, 4-homobrend-3-ylcarbinol (**4**) was transformed predominantly into 4-homoisotwistane (**15**), while 2-methyl-4-homobrendan-2-ol (**11**) gave exclusively a mixture of 1- and 2-methyladamantane. 4-Homobrend-*exo*- and -*endo*-2-ylcarbinol (**9x** and **9n**) afforded both **15** and methyladamantanes. **9x** gave also the simple reduction product *exo*-2-methyl-4-homobrendane (**10x**), whereas **9n** did not give the corresponding product (**10n**). The ratio of **15** to combined 1- and 2-methyladamantane, which represented the relative importance of the ring enlargement process vs. the rearrangement of the 4-homobrendane skeleton in **9x** and **9n,** was much larger for **9x** than for **9n.** The result was successfully interpreted with consideration of the relative stabilities of the intermediate bridged cations involved in the ring enlargement.

We had been looking for synthetic routes to 2,4-bishomobrendane (tricyclo[6.2.1.$0^{4,9}$]undecane, **16**), an unknown compound presumed to intervene in some key steps of the acid-catalyzed skeletal rearrangement of tricycloundecane.[1] Hydride transfer reduction–rearrangement[2] of 4-homobrend-2- and -3-ylcarbinols (tricyclo[5.2.1.$0^{3,8}$]dec-2- and -3-ylcarbinols, **9x, 9n,** and **4,** Scheme I) was thought promising in view of the well-documented ring enlargement of the 2-norbornylcarbinyl to the bicyclo[3.2.1]octyl cation.[3,4] In actuality, however, the method failed to give the hoped-for 2,4-bishomobrendane,[5] but produced 4-homoisotwistane (tricyclo[5.3.1.$0^{3,8}$]undecane, **15**), a twice-rearranged ring enlargement product, together with 1- and 2-methyladamantane. Concomitant formation of methyladamantanes indicated, as discussed below, the ring enlargement to be partly inhibited in 4-homobrendylcarbinols. The only example of the inhibition of ring enlargement in the 2-norbornylcarbinyl system has been reported hitherto by Whittaker[6] for the acetolysis of 3,3-dimethylnorborn-*endo*-2-ylcarbinyl tosylate. The extent of the inhibition of the ring enlargement in the present 4-homobrendylcarbinyl system was found at variance with the structures and configurations of the carbinols, and these results were successfully interpreted in terms of the stability of the bridged cationic intermediate involved in the ring enlargement process.

Results

Synthesis. Three tricyclic carbinols, 4-homobrend-3-, -*exo*-2-, and -*endo*-2-ylcarbinol (**4, 9x,** and **9n,** respectively), as well as 2-methyl-4-homobrendan-2-ol (**11**) of undetermined configuration, were prepared according to the routes shown in Scheme I. Bromination[7] of 4-homobrendane (**1**)[2a,8] gave exclusively the 3-bromide **2.**[8,9] Its structure was determined unequivocally by ^{13}C NMR spectrometry and lithium–*tert*-butyl alcohol reduction. Ten signals including the lowest field singlet in the ^{13}C NMR spectrum indicated the bromide to be an asymmetrical bridgehead-substituted derivative. Reduction by lithium in *tert*-butyl alcohol reverted the bromide back to the original hydrocarbon **1** to demonstrate the intactness of the skeleton during the bromination. Koch carboxylation of **2** gave the corresponding acid **3,** and the structure of **3** was established by the formation of the same 3-ol **5**[10]

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