Concerning the Significance of Product Development Control as an Important Factor in the Reduction and Alkylation of Model Ketone Systems

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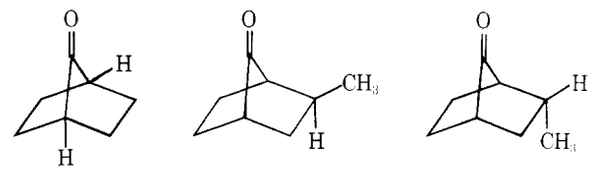
The concept of "product development control" has been used to explain the stereochemistry of many reactions in which the observed isomer ratio reflects the stability of the product. This concept has been used particularly to explain predominant formation of the most stable isomer in reactions of $LiAlH_4$ and MeMgBr with substituted cyclohexanones. A study of the reaction of $LiAlH_4$ and MeMgBr with 7-norbornanone and its *exo*-2-methyl and *endo*-2-methyl derivatives shows that the most unstable isomer is formed exclusively and hence product development control is not a factor in these reactions. In an attempt to broaden the scope of this study, three series of reagents were studied: (1) $LiBH_4$, $LiAlH_4$, and $LiGaH_4$, (2) BH_3, AlH_3, and GaH_3, and (3) $(CH_3)_2Be$, $(CH_3)_2Zn$, $(CH_3)_2Mg$, and $(CH_3)_3Al$. In no case was "product development control" observed. The reactions with the 7-norbornanone system are similar in nature to those with cyclohexanones, except that the complicating factors of torsional strain, compression effect, and conformational changes which are present in cyclohexanone systems are not present in the 7-norbornanone system. The concept of "product development control" is, therefore, a questionable one in ketone reductions involving $LiAlH_4$ and alkylations involving MeMgBr.

In recent years the area of stereoselective reduction and alkylation of ketones by metal hydrides and alkyls has received considerable attention.[1,2] All mechanisms concerning the stereoselective addition or reduction of ketones assume that the entering group approaches the carbonyl carbon on a line perpendicular to the plane of the carbonyl group so that maximum orbital overlap is achieved in the transition state. Dauben and co-workers[3] coined the terms "steric approach control" and "product development control" and suggested that these factors are important in determining the stereochemistry of $LiAlH_4$ reduction of cyclohexanones. Steric approach control implies an early, reactant-like transition state in which the entering group approaches the least hindered side of the ketone whereas product development control implies a late, product-like transition state in which the observed isomer ratio reflects the thermodynamic stability of the product.

The concept of "steric approach control" is generally agreed to be valid since certainly the ability of one molecule to approach another must depend to some extent on the steric requirements of the molecules involved. However, the concept of "product development control" has been questioned by Eliel and co-workers[4-7] on the basis of competitive rate studies involving $LiAlH_4$ and 3,3,5-trimethylcyclohexanone. They have shown that an axial methyl group in the 3 and/or 5 position retards the rate of axial attack compared to 4-*tert*-butylcyclohexanone, whereas the rate of equatorial attack remains essentially the same. This observation is not consistent with that predicted by "product development control" in that an axial methyl substituent would be expected to retard equatorial attack.

As an alternative to "product development control", Cherest and Felkin introduced the concept of "torsional strain"[8-11] and we have developed the concept of "compression effects" to explain the unusual stereochemistry observed in the reactions of $(CH_3)_3Al$ with substituted cyclohexanones.[12] The cyclohexanone ring system may also undergo conformational changes, a factor which has been discussed by Landor and Regan.[13] More recently orbital symmetry arguments[14] and unequal distortion of electron density[15] about the carbonyl group have been suggested to explain the stereochemistry of certain reactions.

Alkylation and reduction studies of a model ketone system in which torsional strain, compression effects, and conformational changes are not possible were carried out so that "steric approach control" and "product development control" could be evaluated independently of these other possible effects. 7-Norbornanone (I) exhibits bridgehead hydrogen atoms



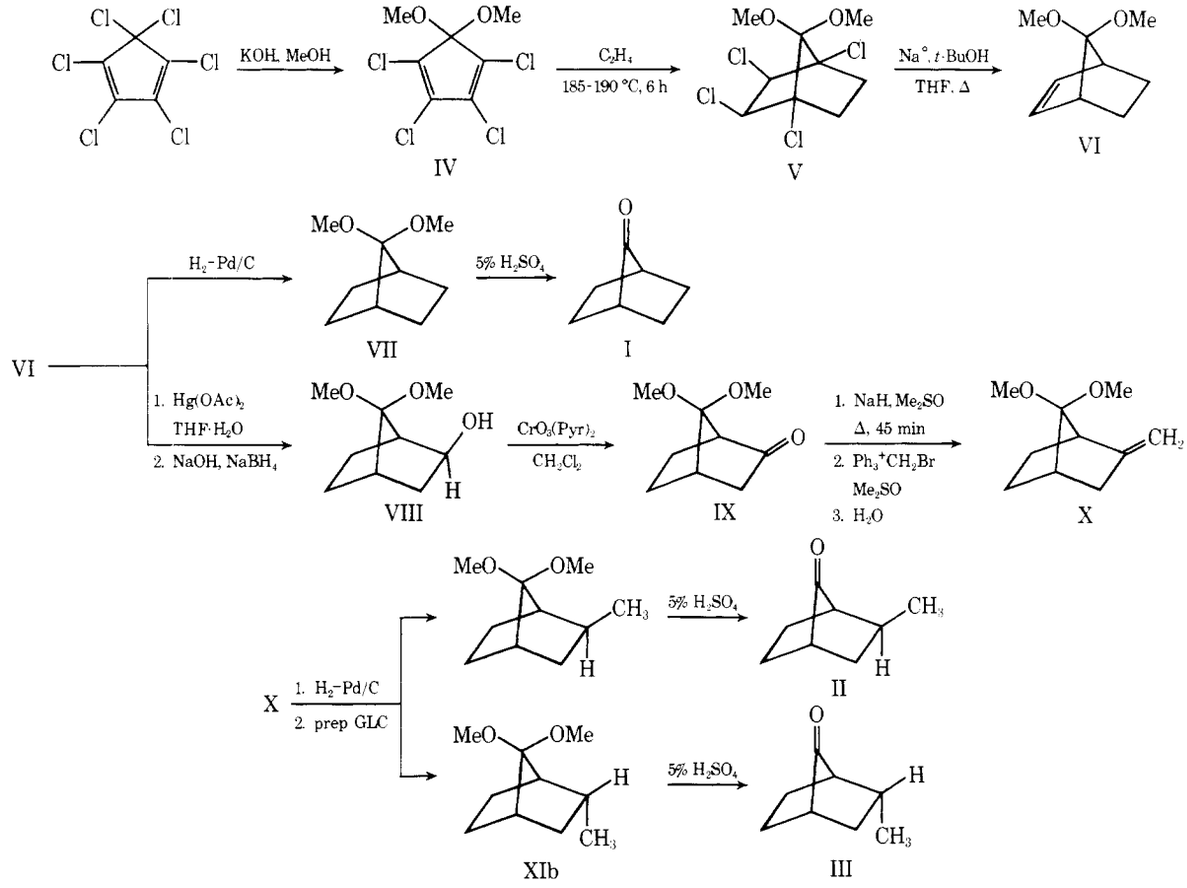
I II III

in the 1 and 4 positions which eclipse the carbonyl group in the 7 position. The unique feature, unlike that of the 2,6-diequatorial hydrogens in cyclohexanone which lie 4–5° below the plane of the carbonyl group, eliminates torsional strain or compression effect as a complicating factor in evaluating stereochemical data obtained from this system. The fact that I is a rigid bicyclic system further eliminates conformational changes in the substrate as a further complicating factor. It is clear then that the validity of the concept of "product development control" involving the reaction of $LiAlH_4$ or methylmagnesium bromide (Grignard reagents) as well as other reducing and alkylating reagents with ketones can be more rigorously tested using this system.

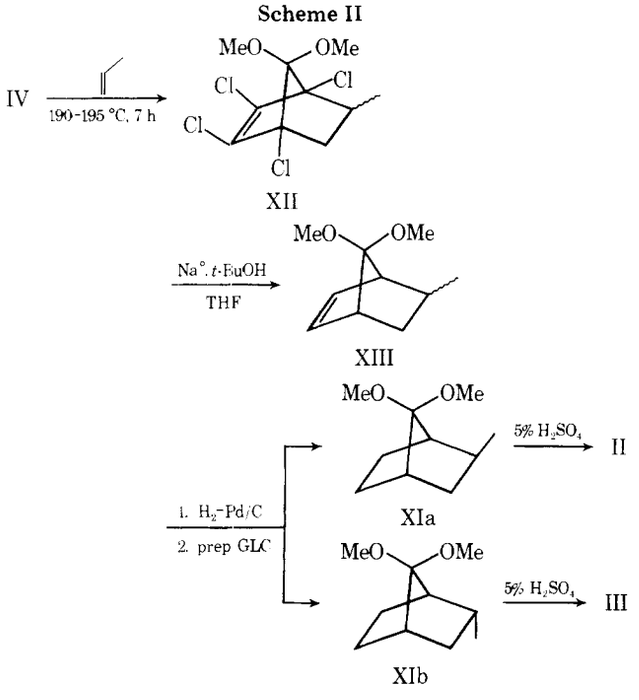
Results and Discussion

Synthesis of Model Systems for Reduction Studies. The synthesis of 7-norbornanone (I) was accomplished by the procedure of Gassman and Pape.[16] *exo*-2-Methyl-7-norbornanone (II) and *endo*-2-methyl-7-norbornanone (III) were prepared in a straightforward manner from 7,7-dimethoxy-2-norbornene (VI) (see Scheme I). Oxymercuration of VI led to an 80% yield of pure *exo*-2-hydroxy-7,7-dimethoxynorbornene (VIII) after distillation. Chromic acid oxidation of the alcohol in pyridine–dichloromethane afforded 7,7-dimethoxynorbornan-2-one (IX) in an 82% yield following distillation. This ketone was then converted to the corresponding methylene compound (X) using methyltriphenylphosphonium bromide and dimsyl sodium in dimethyl sulfoxide. Catalytic hydrogenation (X) gave a 7:1 ratio of II to III following 5% sulfuric acid catalyzed deketalization. The ketone and/or ketals were separated by gas–liquid chromatography on a 15 ft Carbowax 20M column. The NMR showed a chemical shift of δ 0.96 for II and δ 1.10 for III. These values agreed well with those reported previously.[17]

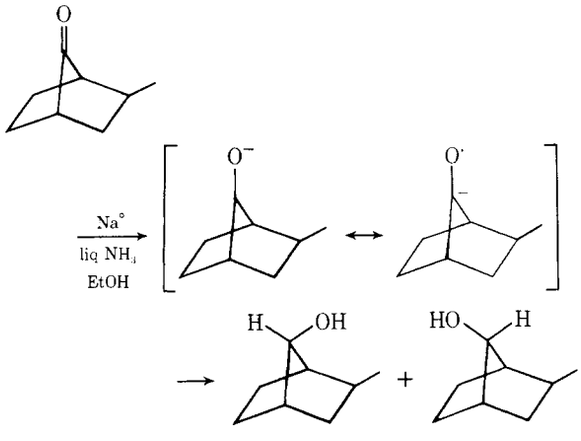
Scheme I



Scheme II



The reduction of ketones I, II, and III was carried out using $LiAlH_4$ as the reducing agent. For a summary of these results, see Table I. The presence of only one alcohol as the reduced product of ketone II was indicated by GLC and ^{13}C NMR. However, it was not possible to determine whether it was the syn or anti alcohol. Therefore, a Birch reduction on ketone II was conducted. Since protonation is faster than equilibration, both the syn- and anti alcohols should be produced (eq 1). It



(1)

An alternate route for the preparation of III was also accomplished as shown in Scheme II. Hexachlorocyclopentadiene was converted into 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (IV) as before. Propylene diluted with nitrogen was added to IV under Diels–Alder conditions giving 5-methyl-7,7-dimethoxy-1,2,3,4-tetrachloronorbornene (XII). XII was then dehalogenated in the presence of sodium metal to give 5-methyl-7,7-dimethoxynorborn-2-ene (XIII). Hydrogenation of XIII gave XIa and XIb in a 1:9 ratio. These ketals were then deketalized to give II and III in a 1:9 ratio.

was observed both by GLC and ^1H NMR that both the syn and anti alcohols were produced in a 20:80 ratio. The alcohols were separated by GLC and found to match the ^1H NMR spectrum reported in the literature.[18] Under Meerwein–Ponndorf–Verley reduction conditions using aluminum isopropoxide and isopropyl alcohol, only the anti alcohol from ketone II was produced. This indicates that under equilibrating conditions the anti alcohol is indeed the most thermodynamically stable product. In order to substantiate this, the syn alcohol was allowed to equilibrate under Meerwein–

Table I. Reactions of $LiAlH_4$ with Ketones I, II, and III in Diethyl Ether and THF[a]

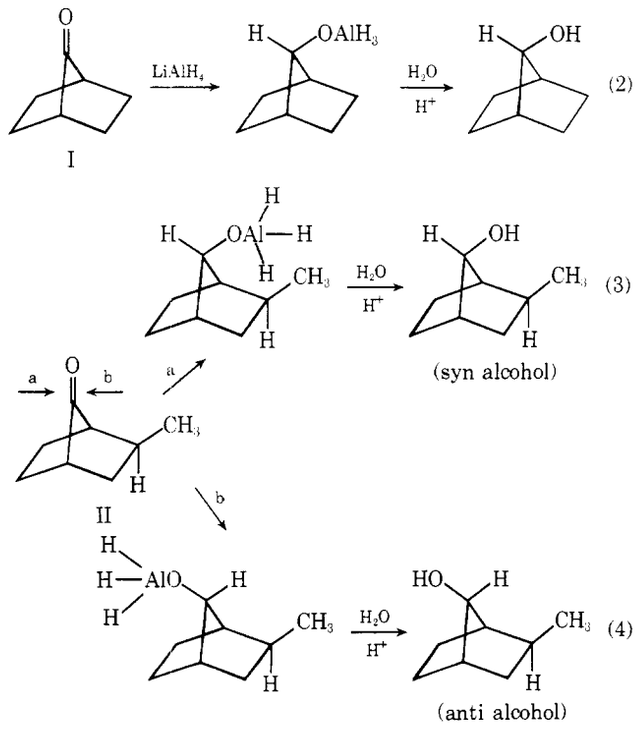
Run	Solvent	Ratio[b] hydride:ketone I	II	III	Recovered[c] ketone, % I	II	III	Products[d] H, OH	H, OH	OH	Mass balance
1	Et_2O	6			0			95.0			95.0
2	Et_2O		6			0			93.7		93.7
3	Et_2O			6			0			92.2	92.2
4	Et_2O	0.25	0.25		60.6	80.4		27.5	13.9		91.2
5	Et_2O	0.25		0.25	70.8		71.8	20.1		20.8	91.8
6	Et_2O		0.25	0.25		74.3	59.0		14.2	28.9	88.2
7	Et_2O	0.11	0.11	0.11	69.3	81.7	71.8	20.6	11.2	19.7	91.4
8	THF		6			0			94.3		94.3
9	THF		0.25	0.25		78.6	61.7		14.9	29.1	92.0
10	Et_2O		0.22	0.11		168.8	72.6		21.3	22.0	94.9
11	Et_2O		0.16	0.04		325.5	81.7		31.2	15.8	90.8
12	Et_2O		0.04	0.16		89.3	321.7		4.1	35.7	90.2

[a] The hydride was added to 0.032 mmol of ketone at 25 °C for 2 h. [b] Hydride:ketone = 6 is equivalent to $LiAlH_4$:ketone mole ratio of 1.5:1. [c] Percent of each ketone recovered based on 100% relative to the amount of hydride added. [d] Percent of each product based on 100% relative to the amount of hydride added.

Ponndorf conditions employing aluminum isopropoxide, isopropyl alcohol, and acetone. The anti alcohol was formed almost exclusively except for a trace of the syn alcohol thus further establishing that the anti alcohol is indeed the thermodynamic isomer.

The ^{13}C NMR spectra of the Birch reduction products were also obtained. By comparing these spectra with the reduction products of $LiAlH_4$ with ketone II, the latter product was confirmed as the syn alcohol. Carbon atom assignments were made by using relative shielding parameters and off-resonance coupling. It is known that deshielding of the carbon decreases from tetrasubstituted carbons to trisubstituted to disubstituted with monosubstituted carbons appearing furthest upfield.

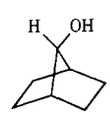
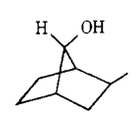
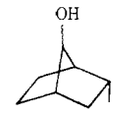
Stereochemistry of 7-Norbornanone Reduction. The reaction of $LiAlH_4$ with I (eq 2) should produce the corresponding alcohol at twice the rate of $LiAlH_4$ reduction of II to produce the syn alcohol (eq 3) provided product development control is not important in this reaction. If product development control is important, then, of course, the rate of attack on II to produce the syn alcohol should be decreased owing to the effect of the *exo*-2-methyl group on the developing transition state (product development control).



Whether or not the *exo*-2-methyl group is sufficiently bulky to exert a valid test for product development control can be evaluated by comparing the syn–anti alcohol ratio when $LiAlH_4$ is allowed to react with II. If the *exo*-2-methyl group exerts a significant steric effect in this system then significally less anti alcohol (eq 4) should be produced compared to the syn alcohol in the reaction of II with $LiAlH_4$. In order to test pertubations on the carbonyl group other than the steric effect exerted by the *exo*-2-methyl group, the reaction of $LiAlH_4$ with *endo*-2-methyl-7-norbornanone (III) was also studied. If only the steric effect of the *exo*-2-methyl group is significant, then the reaction of $LiAlH_4$ with III to produce the syn and anti alcohol should proceed at the same rate as the reaction of $LiAlH_4$ with I and at twice the rate compared to the formation of the *syn*-2-*exo*-methyl alcohol.

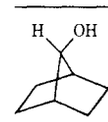
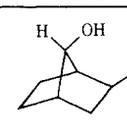
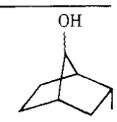
The reductions of I, II, and III were carried out under identical conditions. As noted before, only one reduction product was obtained for I and II, whereas III gave both the syn and anti alcohols according to GLC and ^{13}C NMR. By comparing GLC and ^{13}C NMR, it was substantiated that the lone reduction product of II was the syn alcohol. Table I shows these observations as a result of anti attack with respect to the *exo*-2-methyl group. This shows that the *exo*-2-methyl group exerts a significant steric effect with respect to attack at the 7-keto group since no anti alcohol is observed. When I and II were admixed in equal molar portions with an insufficient amount of $LiAlH_4$, the alcohol products of I and II were produced in a 2:1 ratio indicating no detectable product development control. Reaction of I and III in equal molar portions with an insufficient amount of $LiAlH_4$ produced the corresponding alcohols in a 1:1 ratio showing that the *endo*-2-methyl group has no effect on the rate of reaction of the 7-keto group. Admixture of II and III in equal molar ratio produced the corresponding alcohols in a 1:2 ratio and admixture of I, II, and III in equal molar ratio produced the corresponding alcohols in a 2:1:2 ratio when allowed to react with an insufficient amount of $LiAlH_4$. The data support the conclusion that anti attack on II takes place at the same rate as attack from either side of the carbonyl on I and III indicating that the *exo*-2-methyl group, although exerting a significant steric

Table II. Reactions of MH_3 with Ketones I, II, and III in Diethyl Ether[a]

Run	Reducing agent	Ratio[b] hydride:ketone I	II	III	Recovered[c] ketone, % I	II	III	Products[d] 			Mass balance
1	BH_3		6			0			95.2		95.2
2	BH_3		0.25	0.25		71.8	55.5		15.7	29.3	86.1
3	AlH_3		6			0			96.3		96.3
4	AlH_3		0.25	0.25		70.9	62.7		15.8	30.4	90.0
5	GaH_3		6			0			94.7		94.7
6	GaH_3		0.25	0.25		69.7	54.3		18.0	35.9	89.2

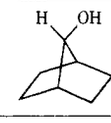
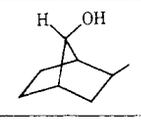
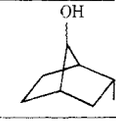
[a] The hydride was added to 0.032 mmol of ketone at 25 °C for 2 h. [b] Hydride:ketone = 6 is equivalent to metal hydride:ketone mole ratio of 2:1. [c] Percent of each ketone recovered based on 100% relative to the amount of hydride added. [d] Percent of each product based on 100% relative to the amount of hydride added.

Table III. Reactions of Complex Metal Hydride of Varying Anion Size with Ketones II and III in THF[a]

Run	Reducing agent	Ratio[b] hydride:ketone I	II	III	Recovered[c] ketones, % I	II	III	Products[d] 			Mass balance
1	$LiBH_4$		6			0			97.2		97.2
2	$LiBH_4$		0.25	0.25		73.5	60.2		15.7	32.0	90.7
3	$LiAlH_4$		6			0			94.3		94.3
4	$LiAlH_4$		0.25	0.25		78.6	61.7		14.9	29.1	92.0
5	$LiGaH_4$		6			0			94.5		94.5
6	$LiGaH_4$		0.25	0.25		75.3	58.5		12.9	25.5	86.3

[a] The hydride was added to 0.032 mmol of ketone at 25 °C for 2 h. [b] Hydride:ketone = 6 is equivalent to complex metal hydride:ketone mole ratio 1.5:1. [c] Percent of each ketone recovered based on 100% relative to the amount of hydride added. [d] Percent of each product based on 100 percent relative to the amount of hydride added.

Table IV. Reactions of Complex Metal Hydrides of Varying Cation Size with Ketones II and III[a]

Run	Reducing agent	Solvent	Ratio[b] hydride:ketone I	II	III	Recovered[c] ketone, % I	II	III	Products[d] 			Mass balance
1	$LiAlH_4$	THF		6			0			94.3		94.3
2	$LiAlH_4$	THF		0.25	0.25		78.6	61.7		14.9	29.1	92.0
3	$NaAlH_4$	THF		6			0			95.7		95.7
4	$NaAlH_4$	THF		0.25	0.25		75.9	59.3		14.7	27.2	89.2
5	NR_4AlH_4	THF–benzene		6			0			94.6		94.6
6	NR_4AlH_4	THF–benzene		0.25	0.25		76.4	58.3		13.6	26.1	87.5

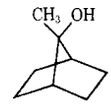
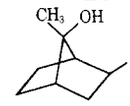
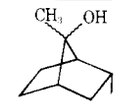
[a] The hydride was added to 0.032 mmol of ketone at 25 °C for 2 h. [b] Hydride:ketone = 6 is equivalent to complex metal hydride:ketone mole ratio 1.5:1. [c] Percent of each ketone recovered based on 100% relative to the amount to hydride added. [d] Percent of each product based on 100% relative to the amount of hydride added.

effect (no anti *exo*-2-methyl alcohol formed, eq 4), does not affect the formation of the syn alcohol of II. When the mole ratio of II to III was increased from 1:1 to 2:1 in the presence of an insufficient amount of $LiAlH_4$ the corresponding alcohols produced were in a ratio of 1:1. This can be explained by the fact that there are now the same number of equal attack sites on both II and III. When the mole ratio of II:III was 4:1, the number of equal attack sites becomes 2:1, and this is indicated by the observation that the ratio of alcohols is 2:1. On the other hand, when the ratio of II:III was 1:4, the number of equal attack sites is 1:8, which is what is reflected in the results of this experiment (Table I). Further experiments in THF and at different stoichiometric ratios provide additional evidence for the above conclusions.

Table II compares the group 3A metal hydrides, AlH_3, BH_3, and GaH_3, reactions with ketones II and III. The results are similar to those observed for $LiAlH_4$ reduction indicating that the stereochemistry is independent of the steric requirement of the hydride. Similarly, when $LiBH_4$, $LiAlH_4$, and $LiGaH_4$ were allowed to react with ketones I–III, no evidence of "product development control" was observed (Table III). In addition when the anion (AlH_4^-) was held constant and the cation varied (Li, Na, NR_4), no evidence of "product development control" was observed (Table IV).

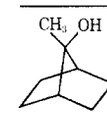
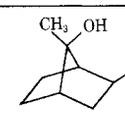
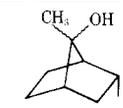
Synthesis of Model Systems for Alkylation Studies. Alkylations of ketones I, II, and III were carried out using methylmagnesium bromide in diethyl ether in an attempt to evaluate the importance of "product development control" when ketones are allowed to react with organometallic alkylating agents. For a summary of these results see Table V. Identification of the products of these reactions is essential just as in the case of the reduction study. The alkylation of ketone II produced only one product as was verified by GLC, ^1H NMR, and ^{13}C NMR. Assuming that the lone alkylation

Table V. Reactions of Methylmagnesium Bromide with Ketones I, II, and III[a]

Run	Solvent	Ratio[b] methyl:ketone I	II	III	Recovered[c] ketone, % I	II	III	Products[d] 			Mass balance
1	Et_2O	6			0			90.3			90.3
2	Et_2O		6			0			95.4		95.4
3	Et_2O			6			0			89.8	89.8
4	Et_2O	0.25	0.25		59.7	78.4		28.3	13.8		90.1
5	Et_2O	0.25		0.25	69.5		70.3	21.2		20.8	90.9
6	Et_2O		0.25	0.25		82.6	63.8		14.9	30.7	96.0
7	Et_2O	0.11	0.11	0.11	70.2	81.0	71.0	20.1	10.8	19.7	90.9
8	Et_2O		0.22	0.11		173.1	76.3		19.8	19.1	96.1
9	Et_2O		0.16	0.04		322.5	82.3		30.6	16.0	90.3
10	Et_2O		0.04	0.16		90.2	330.6		4.4	36.2	92.3
11	THF		0.25	0.25		80.7	61.8		14.2	29.3	93.0
12	THF		6						93.4		93.4

[a] The alkylating agent was added to 0.032 mmol of ketone at 25 °C for 1 h. [b] Methyl:ketone = 6 is equivalent to RMgX:ketone ratio of 6:1. [c] Percent of each ketone recovered based on 100% relative to the amount of alkylating agent added. [d] Percent of each product based on 100% relative to the amount of alkylating agent added.

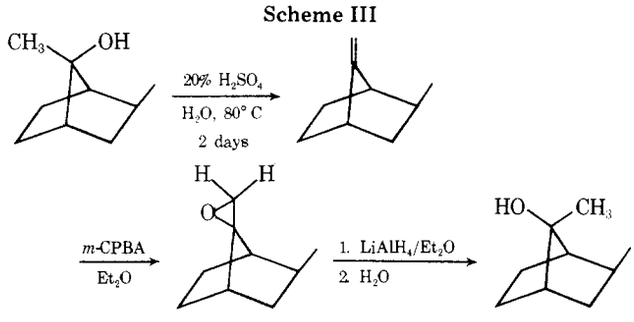
Table VI. Reactions of Metal Alkyls of Varying Steric Requirement with Ketones II and III in Diethyl Ether[a]

Run	Reducing agent	Ratio[b] methyl:ketone I	II	III	Recovered[c] ketone, % I	II	III	Products[d] 			Mass balance
1	Me_2Be		6			0			95.3		95.3
2	Me_2Be		0.25	0.25		83.4	64.3		15.4	31.1	97.1
3	Me_2Mg		6			0			94.6		94.6
4	Me_2Mg		0.25	0.25		80.7	60.1		17.1	33.3	95.6
5	Me_2Zn		6			0			67.3		67.3
6	Me_2Zn		0.25	0.25		65.3	42.8		11.2	20.4	69.8
7	Me_3Al		6[e]			0			65.3		65.3
8	Me_3Al		0.25[e]	0.25[e]		60.2	40.7		10.3	19.6	65.4

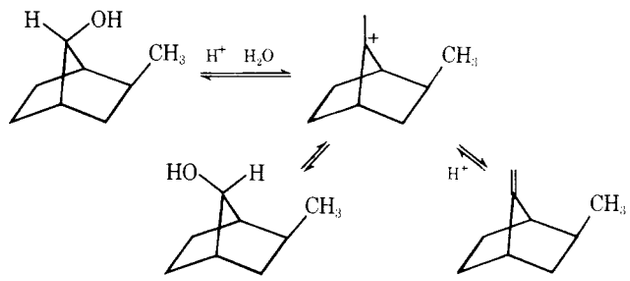
[a] The alkylating agent was added to 0.032 mmol of ketone at 25 °C for 1 hr. [b] Methyl:ketone = 6 is equivalent to R_2M:ketone mole ratio of 3:1. [c] Percent of each ketone recovered based on 100% relative to the amount of alkylating agent added. [d] Percent of each product based on 100% relative to the amount of alkylating agent added. [e] Methyl:ketone = 6 is equivalent to Me_3Al:ketone mole ratio of 2:1.

product was the syn alcohol, the anti alcohol had to be synthesized. A straightforward method to produce the anti alcohol was carried out according to Scheme III. The first step

Scheme III



in this sequence was to dehydrate the tertiary alcohol to the methylene compound followed by epoxidation by *m*-chloroperbenzoic acid which is then followed by $LiAlH_4$ reduction to yield the anti alcohol. However, after periodic monitoring by GLC, it was noted that a second peak appeared with a longer retention time than the starting "syn" alcohol. This second peak continued to grow until it was approximately ⅓ of the starting reactant. This newly formed compound was separated by GLC and identified by ^1H NMR and ^{13}C NMR. By comparing shielding parameters, as was done for the reduction products identification, this second compound was identified as the anti alcohol. The following sequence is postulated to have taken place.



Stereochemistry. The alkylations of I, II, and III were carried out under identical conditions. As noted for the reduction reactions, only one alkylation product was obtained for ketones I and II, whereas ketone III gave both the syn and anti alcohol according to GLC, ^1H NMR, and ^{13}C NMR. Table V shows the results of the alkylation studies with methylmagnesium bromide. In Table VI are recorded the observations of metal alkyl reactions with ketones II and III. Both tables show essentially the same results as noted for the reductions studies conducted with the same ketones. That is, the *exo*-2-methyl group exerts a significant steric effect with respect to attack at the 7-keto group since no anti alcohol is observed. Also, anti attack on II takes place at the same rate as attack from either side of the carbonyl on I or III indicating

that the *exo*-2-methyl group does not affect the formation of the syn alcohol of II. Therefore it can be concluded that product development control in the alkylation reactions of this model ketone system is not important compared to steric approach control.

Experimental Section

Materials. Fisher reagent grade anhydrous diethyl ether was distilled under nitrogen from $LiAlH_4$ prior to use. Fisher reagent grade tetrahydrofuran (THF) was distilled under nitrogen from $NaAlH_4$ prior to use. Hexachlorocyclopentadiene was obtained from Aldrich Chemical Co. and used without further purification.

5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (IV). Hexachlorocyclopentadiene was converted to IV with methanolic potassium hydroxide according to McBee's procedure.[19]

7,7-Dimethoxy-1,2,3,4-tetrachloronorborn-2-ene (V). Under Diels–Alder conditions according to the procedure of Gassman,[16] IV was converted to V with a mixture of ethylene and nitrogen.

7,7-Dimethoxynorbornene (VI). According to the procedure of Gassman and Marshall,[20] V was converted to VI by direct sodium dechlorination.

7-Norbornanone (I). The procedure of Gassman and Pape[16] was followed for the preparation of I which involves the hydrogenation of VI using a palladium on carbon catalyst followed by deketalization using 5% H_2SO_4 or glacial acetic acid to yield I.

***exo*-7,7-Dimethoxynorbornan-2-ol (VIII).** A 500-ml round-bottom flash equipped with a magnetic stirrer was charged with 12.76 g (0.04 mol) of mercuric acetate followed by 40 ml of water. The mercuric acetate dissolved to give a clear solution. Tetrahydrofuran (40 ml) was added to the solution forming a bright yellow suspension. To the mixture, which was cooled in an ice bath, was added 0.038 mol of VI with stirring. The mixture was allowed to warm to room temperature with stirring until the reaction mixture became colorless and clear (30 min). Stirring was continued for an additional 15 min and 40 ml of 3 M sodium hydroxide was added followed by 40 ml of 0.5 M sodium borohydride in 3 M sodium hydroxide. The reduction was almost instantaneous. The mercury was then allowed to settle, and the water layer saturated with sodium chloride. The tetrahydrofuran layer was separated, dried with anhydrous sodium sulfate, and filtered, after which the solvent was removed by rotary evaporation. The crude product was distilled to give 0.030 mol (5.2 g) (79.9%), bp 88–91 °C (6–7 mm).

7,7-Dimethoxynorbornan-2-one (IX). A solution of 16.5 g (0.096 mol) of VIII in 20 ml of dry methylene chloride was added with stirring to the complex formed from 10 g of chromium trioxide and 100 ml of dry pyridine in 100 ml of methylene chloride.[21] After stirring for 2 h, the solvent was decanted and removed by rotary evaporation. The crude product was distilled to yield 13.3 g (0.078 mol), 81.7%, bp 71–72 °C (1–2 mm).

2-Methylene-7,7-dimethoxynorbornane (X). A solution of sodium methylsulfinyl carbanion was prepared according to the procedure of Corey.[22] Into a three-necked, round-bottom flask was placed 3.84 g (0.08 mol) of sodium hydride (50% mineral oil dispersion). The sodium hydride was washed three times with petroleum ether by swirling, allowing the hydride to settle, and decanting the liquid portion in order to remove the mineral oil. The flask was immediately fitted with a magnetic stirrer, a reflux condenser, and a pressure-equalizing dropping funnel. A three-way stopcock, connected to the top of the reflux condenser, was connected to a water aspirator and a source of dry nitrogen. The system was evacuated until the last traces of petroleum ether were removed from the sodium hydride and was then flushed with nitrogen by evacuating and filling the nitrogen several times. The aspirator hose was removed and this arm of the stopcock was connected to a bubbler to which the system is opened. Dimethyl sulfoxide which was distilled from calcium hydride (bp 64 °C, mm) was introduced through the dropping funnel and the mixture was heated with stirring to 70–75 °C until the evolution of hydrogen ceases, which usually was about 45 min. The solution was cooled in a cold water bath and stirred during the addition of 17.8 g (0.077 mol) of (methyl)triphenylphosphonium bromide in 50 ml of warm dimethyl sulfoxide whereupon the deep red color of the ylide was produced. After stiring for 15 min the ketone IX in 10 ml of dimethyl sulfoxide was added with stirring in a cold water bath. The reaction mixture was heated to 60 °C for 4 h. The reaction mixture was then cooled and poured into 500 ml of cold water. The mixture was extracted three times with pentane, washed once with water, dried over anhydrous sodium sulfate, and the solvent removed by rotary evaporation. The crude product was distilled to give 10.0 g (0.06 mol), 77% yield, bp 76–80 °C (15 mm).

2-Methyl-7,7-dimethoxynorbornane (XI). In a hydrogenation flask, X was added to 10 ml of 95% ethanol and 0.3 g of 5% palladium on carbon. This mixture was stirred under hydrogen at room temperature until the amount of hydrogen (1344 ml) had been taken up. The catalyst was removed by filtration, and the crude product was purified and the exo and endo isomers were separated by preparative gas chromatography using a 6 ft × 0.5 in. i.d. 20% Carbowax 20M on Chromosorb W-NAW at 125 °C with a flow rate of 6.5 cm^3/min. The exo ketal XIa was in a ratio of 7:1 with the endo ketal XIb.

***exo*-2-Methyl-7-norbornanone (II).** Into a 50-ml Erlenmeyer flask, the exo ketal XIa was added to 25 ml of 5% H_2SO_4 and stirred for 12 h. The crude ketone was purified by GLC. The ^1H NMR showed a doublet at δ 0.96, J = 6 Hz.

***endo*-2-Methyl-7-norbornanone (III).** The same procedure used above for the preparation of the exo ketone was incorporated in the preparation of III.

5-Methyl-7,7-dimethoxy-1,2,3,4-tetrachloronorborn-2-ene (XII). A mixture of propylene and nitrogen was bubbled into 264 g of IV which had been preheated to 190 °C. After maintaining these conditions for 6 h, the reaction mixture was cooled and distilled to give 229.5 g (75%) of XII, bp 88–91 °C (0.7 mm).

5-Methyl-7,7-dimethoxynorborn-2-ene (XIII). To a vigorously stirred solution of 90 g (1.22 mol) of *tert*-butyl alcohol, 525 ml of dry tetrahydrofuran, and 59 g (2.57 g-atoms) of finely chopped sodium metal under a nitrogen atmosphere was added 30.6 g (0.1 mol) of XII. The mixture was heated gently to maintain a steady reflux for 10 h. After cooling, the excess sodium was destroyed by slow addition of methanol (about 500 ml) to the reaction mixture. The reaction mixture was poured over 2 l. of ice and the reaction flask was washed with approximately 600 ml of water. The solution was extracted with three 250-ml portions of water and once with saturated sodium chloride solution. The ethereal solution was dried over anhydrous sodium sulfate and filtered. The crude product was distilled to give 9.8 g (58.7%), bp 73–78 °C (13 mm).

Hydrogenation of XIII. In a hydrogenation flask, 9.8 g of XIII was added to 10 ml of 95% ethanol and 0.10 g of 5% palladium on carbon. This mixture was stirred under hydrogen at room temperature. After the hydrogen absorption had ceased, the catalyst was removed by filtration. The crude product was purified and the exo and endo isomers were separated by preparative GLC yielding a 9:1 ratio of endo and exo ketals. The spectra of these compounds were identical with those of the exo and endo ketals XIa and XIb prepared above.

Birch Reduction of II. To a 100-ml three-necked round-bottom flask equipped with a magnetic stirrer, dry ice–acetone condenser, and a stopper were added 50 ml of condensed anhydrous ammonia, 0.122 g (0.001 mol) of II, and 2.5 ml of absolute ethanol. To this stirred reaction mixture, 0.7 g of finely chopped sodium metal was added. A deep blue color was produced. Stirring was continued for 15 min and the ammonia allowed to evaporate after the addition of 2.5 ml of water. The mixture was extracted twice with hexane. The combined hexane extracts were washed with water and saturated sodium chloride solution and then dried with anhydrous sodium sulfate. The hexane was removed by rotary evaporation. The residue showed two peaks on the gas chromatograph using a 15-ft, 20% Carbowax 20M on Chromosorb W-NAW column which indicated the syn and anti alcohols in a 20:80 ratio. The syn alcohol has the shorter retention time compared to the anti alcohol. The first alcohol eluting off the column matched the retention time of the alcohol obtained from the reduction of II by $LiAlH_4$. See the Discussion. Also, the ^1H NMR showed two absorptions at δ 4.10 and 3.97—a 20:80 ratio. This together with ^{13}C NMR confirmed that the major product of the Birch reduction of II was the anti alcohol.

Complex Metal Hydride Reductions. A 50-ml Erlenmeyer flask equipped with a magnetic stirring bar was flash flamed under nitrogen and then fitted with a rubber septum. The flask was cooled to 0 °C and 1 ml of 0.032 M ketone in tetrahydrofuran or diethyl ether was added to the flask, along with the internal standard which was hexadecane. The reactions were quenched after 2 h with saturated ammonium chloride and the solvent partially removed under vacuum (Tables I–IV).

Meerwein–Ponndorf–Verley Reduction (II). Into a 50-ml flask fitted with a partial reflux head and a magnetic stirrer were placed 2 ml of a 0.032 M solution of II in diethyl ether along with 1.0 g of aluminum isopropoxide and 5 ml of isopropyl alcohol. This mixture was heated to 50 °C and stirred for 2 days. After cooling to room temperature, the mixture was poured into 100 ml of saturated aqueous ammonium chloride and the solution extracted with two 10-ml portions of ether. The ethereal extracts were combined, washed with water and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The ether was partially removed by use of a

water aspirator. This solution was then analyzed as before by GLC. The only product was the anti alcohol.

Meerwein–Ponndorf Equilibration of II and III. Into a 50-ml round-bottom flask equipped with a magnetic stirrer were placed 100 mg of *syn*-2-*exo*-methyl-7-norbornanol, 1 g of aluminum isopropoxide, 5 ml of isopropyl alcohol, and 5 ml of acetone. Mild heat was applied with stirring for 3 days. The GLC analysis of the hydrolyzed mixture showed the anti alcohol almost exclusively except for a trace of the syn alcohol.

Alkylations of I, II, and III. The same procedure used for the reductions was invoked for the alkylations. All of the products were isolated and identified via ^{1}H NMR, ^{13}C NMR, and GLC.

Acknowledgment. We wish to thank the National Science Foundation for support of this work.

Registry No.—I, 10218-02-7; II, 59532-17-1; III, 59532-18-2; IV, 2207-27-4; VI, 875-04-7; VIII, 10421-72-4; IX, 10265-39-1; X, 60761-81-1; XIa, 60734-22-7; XIb, 60734-23-8; XII, 60734-24-9; XIII, 60734-25-0.

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Thermal and Base-Catalyzed Isomerizations of Birdcage and Half-Cage Compounds

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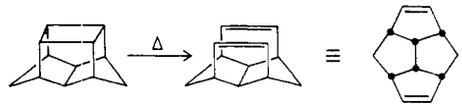
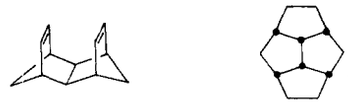
Thermal rearrangements of the birdcage hydrocarbon and alcohol afforded a novel, all-cis fused tetracyclic system containing four five-membered rings. Base-promoted isomerizations of the birdcage alcohol and the half-cage ketone proceeded via a transannular keto–enolization process involving a γ hydrogen to give a new isomeric half-cage ketone.

The birdcage and half-cage compounds[1] have provided attractive frameworks for the study of transannular interactions and for further synthetic investigations.[2] Here, we report new polycyclic systems obtained by thermal and base-promoted[3] isomerizations of these systems.

Thermal Isomerization. Thermal behavior of the birdcage hydrocarbon (1) and its derivatives was initially studied over heated quartz chips using a pyrolytic gas chromatogram unit. Hydrocarbon 1 was stable below 500 °C but between 500 and 650 °C it afforded a mixture of 1 and a new hydrocarbon **3**.[4]



1 3



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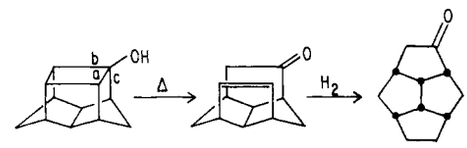
Above 700 °C complete degradation to small fragments resulted. Under preparative conditions over silicon chips, compound **3** was obtained in 27% yield (35% conversion) at 600 °C. No isomerization occurred at 550 °C, and at 650 °C the yield of **3** was about one-half that at 600 °C due to extensive fragmentation. Over platinum, extensive decomposition occurred above 500 °C and naphthalene was the sole identifiable product.

The diene **3** is an air-sensitive, colorless wax, mp 134–136 °C, and the mass spectral fragmentation pattern closely resembled that of **1**. The UV spectrum showed only end absorption. The infrared spectrum contained typical cyclopentene bands[2] at 3040, 1615, and 725 cm^{-1} but was significantly different from that of the isomeric diene **4** (3020, 1566, and 725 cm^{-1}). The ^{1}H NMR spectrum showed a sharp singlet at δ 5.40 (4 H) due to olefinic protons and two broad singlets at 1.95 (4 H) and 3.37 (6 H) due to secondary and tertiary protons, respectively. The diene **3** absorbed 2 mol of hydrogen to give an air-stable, tacky hydrocarbon **5**.

The birdcage alcohol **2** rearranges more readily than **1**. Scouting pyrolysis experiments indicated that **2** rearranged cleanly between 255 and 400 °C to unsaturated ketone **6**.



2 6 7

Between 500 and 600 °C the pyrolysate contained another ketone which had the same retention time and ir as the iso-half-cage ketone **8** (see below), as well as smaller fragments. Above 700 °C complete decomposition was observed. Preparatively **6** was obtained in 79% yield (91% conversion) by feeding an alcoholic solution of **2** over silicon chips at 500 °C. The unsaturated ketone **6** was, like **3**, air sensitive and satisfactory elemental analyses were difficult to obtain. Compound