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Aluminum Hydride Reduction of α-Ketols. II. Additional Evidence for Conformational Flexibility in the Transition State

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The stereochemistry of the reduction with four aluminum hydride reagents of five α-ketols and four α-diones has been studied. The results, together with those of a previous study, representing a total of seven substitutional types, are considered in terms of current models of asymmetric induction in α-ketols. The stereoselectivity observed may be correlated by Cram's cyclic model for asymmetric induction in chiral ketones only with a monomeric reagent, triisobutylaluminum. A modification of Cram's model, wherein the intermediate alanate complex exists in a cyclopentanoid half-chair conformation, allows explication of several observed anomalies. A dependence of the stereoselectivity of the reduction upon the bulk of the reagent is accommodated by this model. Two side reactions, Meerwein–Ponndorf–Verley reduction and hydride-catalyzed keto–hydroxyl isomerization, are considered as alternative reaction paths which might affect observed stereoselectivity. While both reactions are noted under specified conditions, the degree to which each occurs (and in the former case, kinetic considerations) suggests that their effect is minimal.

We have recently reported[1] the results of a study of the reduction of several aliphatic α-ketols of the type I and II (Chart I) with the aluminum hydride reagents, triisobutylaluminum (TIBA), diisobutylaluminum hydride (DIBAH), lithium aluminum hydride ($LiAlH_4$), and lithium trimethoxyaluminum hydride (LTMAH). These systems were found to conform to Cram's cyclic model[2] for asymmetric induction in chiral ketones to the extent that, in each case, the predominant isomer formed was the predicted erythro isomer. The degree of stereoselectivity found, however, did not correlate well with α-ketol structure in the presumed cyclic transition state A (Chart II) in which the aluminum-bound ligands are symmetrically disposed on either side of the five-membered chelated ring. To account for the peculiar variations in observed stereoselectivity, and to account for an indicated role of the attacking hydride reagent in determining preferred transition state geometries, we suggested that certain conformations of the chelated ring, *e.g.*, the cyclopentanoid half-chair configurations B and C (Chart II) first proposed by Stocker,[3] provided an improved basis for the rationalization of noted anomalies.

Chart I

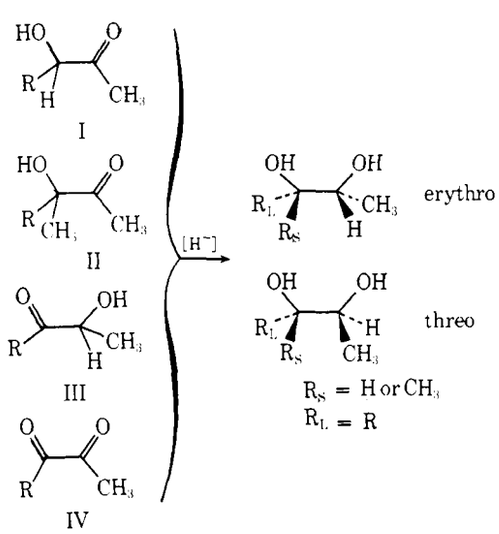
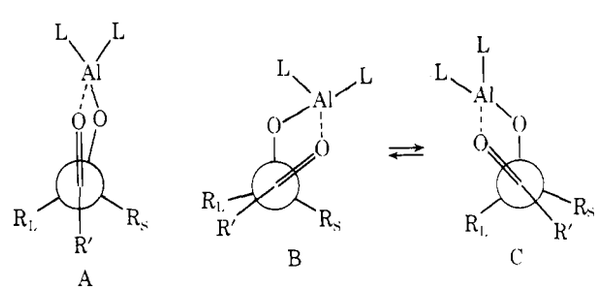
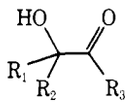


Chart II

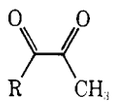


We wish to report the results of studies of the reduction of α-ketols of the type III and the corresponding α-diones IV (Chart I) with the above aluminum hydride reagents. As will be described, the results support our contention that the transition state geometry of the aluminum chelate in the reduction is satisfactorily represented by an equilibrium of the conformers B and C (Chart II).[1] Evidence is also presented that two possible side reactions which might influence observed stereoselectivity, Meerwein–Ponndorf–Verley reduction and hydride-catalyzed keto–hydroxyl isomerization, have only a minimal effect on the steric course of the reaction.

Table I
Yield of Diol Products and Per Cent Erythro Isomer Produced in the Hydride Reduction of Substrates



α-ketols (types I, II, III)



α-diones (type IV)

Registry no.	Compd	Substituents[a] R1	R2	R3	% erythro[b] (diol yield %)[c] TIBA (toluene)	DIBAH (toluene)	$LiAlH_4$ (THF)	$LiAl(OMe)_3H$ (THF)
52279-26-2	1	CH_3	H	n-C_5H_{11}	49 (69)	64 (90)	64 (98)	73 (94)
52279-27-3	2	CH_3	H	i-Pr	71 (71)	55 (83)	58 (78)	46 (98)
52278-28-4	3	CH_3	H	t-Bu	89 (65)	64 (87)	87 (79)	85 (98)
5650-40-8	4	CH_3	H	Ph	66 (83)	60 (94)	87 (92)	85 (98)
90-63-1	5	Ph	H	CH_3	83 (70)	79 (72)	80 (85)	76 (85)
585-25-1	6	n-C_5H_{11}			57 (69)	62 (83)	54 (92)	54 (87)
7493-58-5	7	i-Pr			85 (69)	59 (75)	60 (91)	53 (84)
40898-19-9	8	t-Bu			96 (86)	68 (87)	74 (98)	71 (92)
579-07-7	9	Ph			76 (70)	77 (74)	72 (98)	78 (99)

[a] Substitution as in figures above; in compounds 6–9, R_1 refers to R in the dione structure. [b] Nmr analysis (see ref 1). [c] Isolated yield of diol, *ca.* 95% pure.

Table II
Stereoselectivity Observed in Reductions of α-Ketols and α-Diones

Compd	Substituents[a] R1	R2	R3	Stereoselectivity[b] (diastereomer ratio)[c] TIBA (toluene)	DIBAH (toluene)	$LiAlH_4$ (THF)	$LiAl(OMe)_3H$ (THF)
			Disubstituted α-Ketols, Type III				
1	CH_3	H	n-C_5H_{11}	−2 (0.96)	28 (1.78)	28 (1.78)	46 (2.70)
2	CH_3	H	i-Pr	42 (2.44)	10 (1.22)	16 (1.38)	−8 (0.85)
3	CH_3	H	t-Bu	78 (8.09)	28 (1.78)	74 (6.69)	70 (5.67)
4	CH_3	H	Ph	32 (1.94)	20 (1.50)	74 (6.69)	70 (5.67)
			Disubstituted α-Ketols, Type I				
d	n-C_5H_{11}	H	CH_3	8 (1.17)	36 (2.13)	40 (2.33)	56 (3.55)
d	i-Pr	H	CH_3	66 (4.88)	24 (1.63)	46 (2.70)	32 (1.94)
d	t-Bu	H	CH_3	>96 (49)	46 (2.70)	50 (3.00)	54 (3.35)
5	Ph	H	CH_3	66 (4.88)	58 (3.76)	60 (4.00)	52 (3.16)
			α-Diones, Type IV				
6	n-C_5H_{11}			14 (1.33)	24 (1.63)	8 (1.17)	8 (1.17)
7	i-Pr			70 (5.67)	18 (1.44)	20 (1.50)	6 (1.13)
8	t-Bu			92 (24.0)	36 (2.13)	48 (2.84)	42 (2.44)
9	Ph			52 (3.16)	54 (3.35)	44 (2.57)	56 (3.55)
			Trisubstituted α-Ketols, Type II				
d	i-Pr	CH_3	CH_3	70 (5.67)	42 (2.45)	−2 (0.96)	20 (1.50)
d	t-Bu	CH_3	CH_3	82 (10.11)	20 (1.50)	28 (1.78)	40 (2.33)
d	Ph	CH_3	CH_3	64 (4.56)	56 (3.55)	34 (2.03)	14 (1.33)

[a] Substitution as in the figures above, Table I; in compounds 6–9, R_1 refers to R in the dione structure. [b] Stereoselectivity = % erythro − % threo isomer. [c] Diastereomer ratio = % erythro/% threo isomer. [d] Data taken from ref 1.

Results

The substrates 1–9 were reduced in good yields by the aluminum hydride reagents under the same conditions used in our previous study.[1] Quantitation of the erythro isomer in each mixture was accomplished by the nmr technique described; chemical shift data used for these measurements were those previously reported.[1] Stereochemical assignments for the phenyl-substituted systems (**4**, **5**, and **9**), which were not incorporated in our earlier work, were confirmed by comparison to authentic samples of *erythro*- and *threo*-1-phenyl-1,2-propanediol, prepared by trans and cis hydroxylation of isomerically pure *trans*-phenylpropene.

The yields of the product α-diols and the per cent erythro isomer in each mixture are presented in Table I. Stereoselectivity and isomer ratios calculated from these data are presented in Table II, together with the findings of our previous work.[1]

General Observations. Examination of Table II reveals several striking features of the data. Of the reagents, TIBA alone affords the anticipated regular increase of stereoselectivity with increasing bulk of R (Chart I) for all of the

cases studied; $LiAlH_4$ exhibits the same property, albeit to a lesser degree, except in the case of α-ketols of type III (1–4). The results of reduction of phenyl-substituted systems with TIBA are at curious variance with those of other reagents. In the reduction with TIBA, the steric bulk of the phenyl group appears comparable to or smaller than that of the isopropyl group, while with other reagents, the bulk of the phenyl group would seem to be equal to or greater than that of the *tert*-butyl group.

In other respects, the data appear to be poorly correlated. The stereoselectivities of the reduction of trisubstituted systems (final three entries) with DIBAH and LTMAH are badly scattered; for the disubstituted α-ketols and α-diones, however, a recognizable pattern emerges. In many cases the selectivity of the isopropyl-substituted system is less than that of the *n*-pentyl system. Change of R to the *tert*-butyl group reverses this trend, and the stereoselectivity observed is comparable to and usually greater than that of the *n*-pentyl system.

Discussion

Steric Effects Influencing the Stereoselectivity of Reduction. Any model advanced to correlate the data of Table II must include features which allow a role for the attacking hydride reagent in creating preferred transition state geometries, as well as sufficient conformational flexibility of the aluminum chelate to explain the anomolous decrease in stereoselectivity in the reduction of the α-ketols with the medium-sized substituent (R = isopropyl) *vs.* those with the smaller substituent (R = *n*-pentyl). Cram[2] has suggested that a decrease of stereoselectivity noted in reactions with lithium reagents upon change of solvent from ether to pentane is due to the intervention of certain dipolar model[4] transition states, made favorable by increased steric crowding of the cyclic transition state, as well as relief of dipolar repulsions. Under this scheme, however, a regular *decrease* in stereoselectivity relative to the predictions of the cyclic model should be observed in a sterically homologous series with a given reagent; this is clearly not the case.

Our previously postulated[1] model (Chart II) does, however, fulfill the above criteria. While several possible conformational equilibria may be possible, equilibration of conformers of the type B and C allows the simplest rationalization of the results shown in Table II. Thus, increase of R_L from *n*-pentyl to isopropyl would destabilize conformer B with respect to C, due to increased interactions of R_L with the carbonyl-bound stubstituent R′. Observed stereoselectivity would then depend on the relative steric interactions of the approaching hydride reagent with R_L and with the ligands attached to the chelated aluminum. For relatively small ligands and a monomeric reagent (TIBA),[5] attack from the upper right to afford the erythro isomer is favored. In the case of DIBAH, where the chelated species is equivalent to that derived from TIBA, the noted decrease in stereoselectivity may be attributed to the greater interactions between the much bulkier, associated (trimeric)[6] attacking reagent and the chelated aluminum, making attack from the lower left to afford the threo isomer somewhat more favorable. Increase in the bulk of R_L to *tert*-butyl would again favor the conformer C; in this case, however, R_L is sufficiently large to make attack from the lower left unfavorable, and an increase in the stereoselectivity of the reduction (relative to R_L = isopropyl) is noted.

Several additional lines of evidence may be advanced to support our contention of the half-chair conformation equilibrium. In studies of the reactions of trimethylaluminum with substituted cycloalkanones, Ashby[7] has recently formulated an alternative model to the traditional "steric approach control" and "product development control" rationales of the stereochemical course of the reductive alkylation of these systems. From Ashby's analysis emerges a point relevant to the case of the reduction of α-ketols: the effective bulk of the carbonyl is increased by complexation with an organoaluminum species to the extent that severe interactions with groups on adjacent carbons may occur in the transition state.[7] Ashby has dubbed this a "compression" effect, as opposed to eclipsing or torsional effects characteristic of single-bond repulsions. Whether α-ketols are subject to compressive *vs.* torsional effects is academic; the salient feature of the argument is that the increased bulk of the carbonyl, together with the large van der Waals radius of the neighboring alkoxide, ensures that the chelated ring will adopt conformations in which the O—C—C=O unit is not planar, *e.g.*, the half-chair conformations B and C.

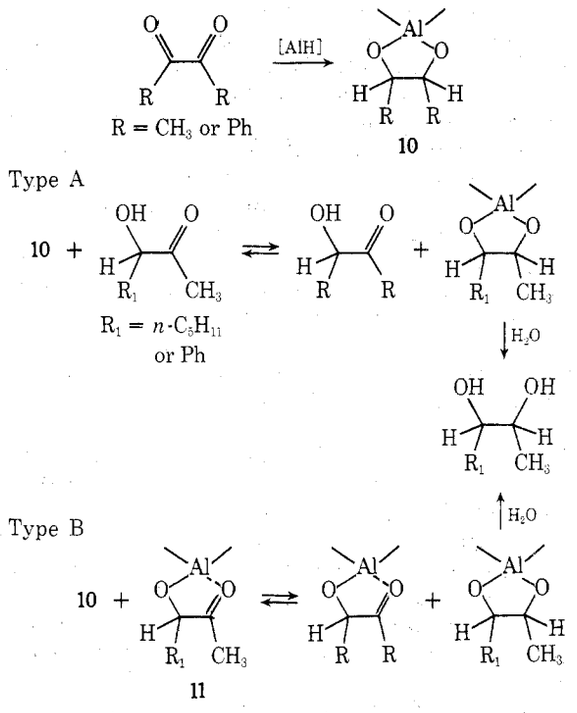
The role of the carbonyl-bound substituent in creating preferred transition state geometries may be inferred from the work of Karabatsos[8] and Felkin[9] with systems following the open-chain[10] model, and is clearly demonstrated by comparison of the stereoselectivity of the reduction of disubstituted α-ketols of types I[1] and III (1–4; Chart I). That the stereoselectivity of the former exceeds that of the latter in 12 of the 16 cases studied is reasonable inasmuch as, in α-ketols of type I, the tetrahedral carbinol carbon allows interaction of R with both the approaching hydride reagent and the carbonyl-bound methyl group to determine a preferred conformation, whereas with α-ketols of type III, interactions of the carbonyl-bound substituent with the β-methyl group alone are those which are anticipated to create a preferred transition state geometry.

Stocker[3] has noted that, in reactions of symmetrically substituted α-diones with organolithium and Grignard reagents, the stereoselectivity observed is the same as that in the reaction of the corresponding trisubstituted α-ketol. The stereoselectivity observed in the reduction of the α-diones 6–9 could, therefore, be the same as that of either the disubstituted α-ketols of types I or III. In any case, the stereoselectivities of the α-ketol reductions, irrespective of their precise transition state geometries, should represent limiting values for the reduction of the corresponding α-dione, as reduction of the latter would presumably be partitioned between the transition states obtained in the α-ketol reductions. Twelve of the sixteen cases studied do indeed conform to this relation.

While the half-chair model provides an adequate rationale to explain many of the unanticipated results in Table II, the behavior of phenyl-substituted systems is clearly outside the predictive domain of the model. The apparent variable effective steric bulk of the phenyl substituent is puzzling, and we have been unable to account for this. For example, an attractive hypothesis which would explain the low stereoselectivity obtained in reductions of substrates possessing the benzoyl moiety with TIBA might be that in these systems the phenyl and carbonyl groups are coplanar, allowing maximum π overlap; in these conformations interactions of the phenyl group with R_L (Chart II) and the attacking hydride reagent would be presumably smaller than in other conformations. The effect is not general, however; in reduction of the same substrates with $LiAlH_4$ and LTMAH, substantially greater stereoselectivities are observed. The effect of the electronic properties of phenyl-substituted systems, as opposed to purely steric factors, is, therefore, a point of continued interest.

Nonsteric Factors Influencing the Stereochemistry of Reduction. Meerwein–Ponndorf–Verley Reduction. Haubenstock and Davidson[11] and Ashby[12] have reported the time-dependent distribution of isomeric cyclohexanols

Chart III



from the reduction of 3,3,5-trimethylcyclohexanone with TIBA as the limiting reagent, and have attributed the observed equilibration to the Meerwein–Ponndorf–Verley reduction—Oppenhauer oxidation scheme. To determine whether the aluminum alkoxides formed in the course of reduction of α-ketols are capable of promoting such reaction, the following experiments were undertaken.

Selected α-ketols were subjected to treatment with aluminum alkoxides analogous to those presumed to be intermediates in the α-ketol reductions (Chart III). The desired alkoxide (**10**) was generated by reduction of benzil (representative of secondary benzylic carbinols) or biacetyl (representative of aliphatic carbinols) with the stoichiometric amount of hydride reagent at room temperature; the substrate was introduced at −78°, and the mixture equilibrated for 24 hr at 25° (type A). Alternatively, addition of the substrate at −78° to solutions of **10** which contained 1 equiv of hydride gave a mixture of substrate as its aluminum derivative (**11**) and **10**, which was equilibrated as above (type B). Separate experiments established that no appreciable reduction of the substrate took place at −78° in this experiment. The use of 1,2-diphenyl-1,2-ethanediol instead of benzil in the generation of the aluminum alkoxide, even at greater than the stoichiometric amount, had no material effect on the observed amount of reduction of the substrate (Table III).

Hydrolysis of the mixtures and analysis of the crude products by glpc gave the results shown in Table III. As opposed to our previous experience with analysis of diol mixtures by glpc,[1] the use of a glass column for these analyses gave highly reproducible results, indicating that decomposition of the diols was minimal. The diastereomeric products were not resolved in the system used, however. While the diol resulting from reduction of the substrate was the only material quantitated, species arising from hydrolysis of the reagent alkoxide (hydrobenzoin or butanediol), oxidation of the reagent alkoxide (benzoin or acetoin) and unreacted substrate were found in each mixture.

The data of Table III correlate in three ways. First, substantially greater reduction is noted in reactions of DIBAH *vs.* $LiAlH_4$. Although there is insufficient information to

Table III
Meerwein–Ponndorf–Verley-like Reduction of α-Ketols

α-Ketol[a] R_1	Reducing agent[b] (solvent)	Alkoxide[a] R	Ratio[c] (type)	Reduction, %
n-C_5H_{11}	DIBAH	CH_3	1:2[d] (A)	16.8
	(toluene)		1:3[e] (B)	35.9
	$LiAlH_4$		2:1[d] (A)	3.1
	(THF)		1.5:1[e] (B)	5.5
Ph	DIBAH		1:2 (A)	16.5
	(toluene)		1:3 (B)	24.5
	$LiAlH_4$		2:1 (A)	4.7
	(THF)		1.5:1 (B)	7.0
	DIBAH	Ph	1:1.5[f]	(34.6)[g]
	(toluene)		1:2 (A)	32.6 (31.8)
			1:3 (B)	53.3 (54.9)
	$LiAlH_4$		2.5:1[f]	(10.5)
	(THF)		2:1 (A)	10.0 (10.6)
			1.5:1 (B)	18.1 (18.4)

[a] Substitution per Chart III. [b] Reagent from which the aluminum alkoxide was prepared. [c] Mole ratio of starting dione to reducing agent to give **10**. Type A, stoichiometric hydride used in preparation of **10**; type B, 1 equiv of excess hydride used (see Chart III). [d] This ratio represents the case in which the α-ketol is not bound to the aluminum alkoxide at the start of equilibration. [e] This ratio represents the case in which the α-ketol is bound to the aluminum alkoxide at the start of equilibration. [f] This ratio represents an excess of the dione relative to the reducing capacity of the hydride reagent. [g] Numbers in parentheses are the reductions noted when the alanate complex was generated from 1,2-diphenyl-1,2-ethanediol rather than benzil.

permit a precise formulation of the alkoxide **10** in these two cases, the more reactive one, derived from DIBAH, is presumed to be neutral and trivalent; the less reactive one, from $LiAlH_4$, anionic and tetravalent (ate complex). Second, reduction is more efficient by secondary benzylic alkoxides than by aliphatic alkoxides; this is thought to represent the difference in the stabilities of the oxidized ligands, the benzylic ketone being stabilized relative to the aliphatic ketone by conjugation with the phenyl ring. Finally, substrates bound to the aluminum species (type B) are reduced more efficiently than the free substrates (type A).

While these results are suggestive, it should be noted that the conditions for the reactions from which the data of Table II are derived differ fundamentally from those above in that the hydride reagent is present in excess throughout the reaction. Haubenstock[11] noted that in the reaction of 3,3,5-trimethylcyclohexanone with TIBA, when TIBA was in excess, no measurable amount of ketone was observed. The presence of ketone is, however, necessary for diastereomer equilibration to occur *via* the MPV reduction–Oppenhauer oxidation mechanism. Thus, in order for MPV reduction to significantly alter the ratio of products arising from direct hydride reduction requires that the rates of MPV reduction and direct hydride reduction be of the same order. As most hydride reductions are very rapid, intuition argues that this is not the case. Furthermore, the results of deuterium scrambling studies (*vide infra*) indicate that the contribution of MPV reduction is limited to, at most, a few per cent. In the absence of suitable kinetic measurements, the precise degree of MPV reduction must remain conjectural.

Hydride Catalyzed Keto–Hydroxyl Isomerization. A second possible reaction which might affect observed stereoselectivity is keto–hydroxyl isomerization of disubstituted α-ketols prior to reduction. The isomerization of α-ketols under the influence of base has been well studied.[13] Of particular interest are the findings of Temnikova,[14] who noted

Table IV
Keto–Hydroxyl Isomerization of α-Ketols

Substituents[a]			Isomerization, %	
R_1	R_2	R_3	$LiAlD_4$	$LiAl(OMe)_3D$
n-C_5H_{11}	H	CH_3	1.2 (0.13)[b]	5.3 (0.30)
Ph	H	CH_3	0.0 (0.13)	0.8 (0.35)
CH_3	H	Ph	1.4 (0.47)	7.7 (1.6)

[a] Substituents are as in the α-ketol structure above Table I. [b] Numbers in parentheses are the average deviations of replicate experiments.

that reaction of 1-(4-tolyl)-2-propanon-1-ol with either ethyl or phenyl Grignard gives, in addition to the expected product, a significant amount of material in which the Grignard reagent has added to the carbinol center, and our own observation that reaction of ethyllithium with 2-octanon-3-ol affords both the anticipated 3-methyl-3,4-nonanediol and 3-ethyl-2,3-octanediol.[15] The anomalous products in both studies can arise only by isomerization of the α-ketol prior to addition to the carbonyl, although the mechanism remains to be elucidated.

To determine whether such isomerization may occur in the course of the hydride reduction of α-ketols, the reduction of three substrates with lithium aluminum deuteride and lithium trimethoxyaluminum deuteride was studied. The reductions were carried out under the same conditions as used for the reduction studies involving the protio reagents. After the usual isolation, the product diols were cleaved with sodium metaperiodate in aqueous tetrahydrofuran, and the major aldehyde (corresponding to R_L of the product diol; Chart I) was isolated as its 2,4-dinitrophenylhydrazone derivative. Isotope ratio mass spectrometry was used to measure the amount of deuterium on the aldehyde carbon; from these data the degree of transposition was determined. The results of this experiment appear in Table IV.

While significant amounts of transposition are noted in most cases, the degree of transposition is considerably less than that which would, in itself, account for the anomalies of Table II. Oddly enough, 1-phenyl-1-propanon-2-ol gives substantially more isomerization than does 1-phenyl-2-propanon-1-ol, in direct opposition to expectations based on Temnikova's findings.[14] The reason for this is not known.

The results of these experiments militate against the intervention of MPV reduction considered above. If MPV reduction of α-ketols was operative under these conditions (excess hydride), one would anticipate substantially greater amounts of deuterium scrambling in the present study than is observed.

Conclusions

The results of the studies of this work and our previous report[1] lend support to the contention of the cyclopentanoid half-chair conformations B and C (Chart II) as the simplest models for the transition state of the reduction of α-ketols. While the model suffices to explain retrospectively a number of unanticipated results, its predictive value, in terms of the degree of stereoselectivity observed, is low, due to the several complex interactions giving rise to the observed products.

Of anticipated side reactions which might affect the stereoselectivity of the reduction in the presence of excess hydride, Meerwein–Ponndorf–Verley reduction would not seem to have any measurable effect, although this point remains to be proven unequivocally. Hydride catalyzed keto–hydroxyl isomerization, however, would appear to have some effect, insofar as the starting α-ketol and its transposition product represent distinctly different steric cases in the reduction. This effect is, however, markedly substrate and reagent dependent, and would account for deviations of only some few per cent of stereoselectivity.

Experimental Section

General. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined in $CDCl_3$ solution on Varian A-60A or HR-220 spectrometers; chemical shift data are reported in parts per million downfield from internal tetramethylsilane (δ scale). Isotope ratio mass spectrometry was performed on a Varian-MAT CH-5 spectrometer. Gas–liquid chromatography was performed on a Hewlett-Packard Model 5750B chromatograph equipped with flame ionization detectors, using a 6 ft × 0.125 in. glass 3% Carbowax 20M on 100/120 Gas-Chrom Q column, and nitrogen as carrier gas.

Glassware for reactions involving organometallic reagents was dried for a minimum of 3 hr at 120°; these reactions were carried out in an atmosphere of dry nitrogen. Solutions were dried over magnesium sulfate unless otherwise indicated.

Tetrahydrofuran (THF) solutions of lithium aluminum hydride and lithium trimethoxyaluminum hydride, and toluene solutions of diisobutylaluminum hydride and triisobutylaluminum were prepared as previously described.[1] Lithium aluminum deuteride (99 atom % deuterium) was obtained from E. Merck, Darmstadt; this reagent and lithium trimethoxyaluminum deuteride were used at THF solutions prepared by the method of Brown.[16]

1-Phenyl-1,2-propanedione (9) was obtained from Aldrich Chemical Co. and was distilled before use. *trans*-Phenylpropene was obtained from Chemical Samples Co. and was used as supplied. Those α-ketols and authentic specimens of isomerically pure diols whose preparations are not herein reported, were from the collection previously described.[1]

Preparation of α-Ketols. The α-ketols 1–4 were prepared by condensation of the appropriately substituted 2-lithio-1,3-dithiane with acetaldehyde, and hydrolysis of the α-hydroxy dithioketal thus produced as previously described.[1]

3-Octanon-2-ol (1). The compound was prepared from 2-*n*-pentyl-1,3-dithiane[17] in 30% yield: bp 62–65° (0.45 mm); oxime mp 61–62° (petroleum ether) [lit.[18] oxime mp 62–63° (aqueous ethanol)]; nmr δ 4.12 (q, J = 7 Hz, 1 H), 3.65 (s, 1 H), 2.49 (t, 2 H), 1.8–1.1 (m, 6 H), 1.31 (d, J = 7 Hz, 3 H), and 0.91 (t, 3 H).

4-Methyl-3-pentanon-2-ol (2). The compound was prepared from 2-isopropyl-1,3-dithiane[17] in 31% yield: bp 64–66° (22 mm); 2,4-dinitrophenylhydrazone mp 148–151° (aqueous ethanol) [lit.[19] bp 51–53° (11 mm); 2,4-dinitrophenylhydrazone mp 151–152° (aqueous methanol)]; nmr δ 4.37 (q, J = 7 Hz, 1 H), 3.30 (s, 1 H), 2.87 (m, J = 7 Hz, 1 H), 1.31 (d, J = 7 Hz, 3 H), 1.12 (d, J = 7 Hz, 3 H), and 1.10 (d, J = 7 Hz, 3 H).

4,4-Dimethyl-3-pentanon-2-ol (3). The compound was prepared from 2-*tert*-butyl-1,3-dithiane[17] in 43% yield: bp 67–69° (11 mm) [lit.[20] bp 102–103° (100 mm)]; nmr δ 4.48 (q, J = 7 Hz, 1 H), 3.27 (s, 1 H), 1.26 (d, J = 7 Hz, 3 H), and 1.17 (s, 9 H).

1-Phenyl-1-propanon-2-ol (4). The compound was prepared from 2-phenyl-1,3-dithiane[17] in 37% yield: bp 75–77° (0.4 mm) [lit.[19] bp 125–126° (13 mm)]; nmr δ 8.0–7.6 (m, 2 H), 7.6–7.2 (m, 3 H), 5.04 (q, J = 7 Hz, 1 H), 3.63 (s, 1 H), and 1.38 (d, J = 7 Hz, 3 H).

1-Phenyl-2-propanon-1-ol (5). Benzaldehyde (10.6 g, 0.10 mol) was added to a stirred suspension of sodium acetylide[21] (*ca.* 0.1 mol) in 200 ml of refluxing ammonia over a period of 1 hr. The mixture was refluxed for an additional 2 hr before quenching by the cautious addition of 10 g of solid NH_4Cl. The ammonia was allowed to evaporate, and the residue was taken up in brine. Three ether extracts of the brine were washed with two portions of saturated $NaHSO_3$ and once with brine and were dried; the solvent was removed.

The crude propynol was hydrated by reaction with 5% H_2SO_4 in the presence of HgO, as previously described.[1] There was obtained 2.4 g (16%) of material: bp 112–115° (17 mm); 2,4-dinitrophenylhydrazone mp 172–174° (aqueous dimethylformamide) [lit.[19] bp 115–119° (16 mm); lit.[22] 2,4-dinitrophenylhydrazone mp 174° (ethanol)]; nmr δ 7.15 (s, 5 H), 4.86 (s, 1 H), 4.07 (s, 1 H), and 1.94 (s, 3 H).

Preparation of α-Diones. The α-diones used in this study were prepared by oxidation of the corresponding α-ketol with chromium trioxide–bispyridine complex in dichloromethane using the procedure of Radcliffe and Rodehorst[23] without modification.

2,3-Octanedione (6). The compound was prepared from 2-octa-

non-3-ol (1) in 33% yield: bp 65–67° (17 mm); bis-2,4-dinitrophenylhydrazone mp 221–224° (aqueous ethanol) [lit.[24] bp 172–173° (733 mm); lit.[25] bis-2,4-dinitrophenylhydrazone mp 221°]; nmr δ 2.68 (t, J = 7 Hz, 2 H), 2.25 (s, 3 H), 1.7–1.1 (m, 6 H), and 0.91 (t, 3 H).

4-Methyl-2,3-pentanedione (7). The compound was prepared from 4-methyl-2-pentanon-3-ol (2) in 33% yield: bp 113–116° (760 mm) (lit.[26] bp 115–116°); nmr δ 3.33 (m, J = 7 Hz, 1 H), 2.25 (s, 3 H), and 1.07 (d, J = 7 Hz, 6 H).

4,4-Dimethyl-2,3-pentanedione (8). The compound was prepared from 4,4-dimethyl-2-pentanon-3-ol (3) in 61% yield: bp 123–127° (760 mm); bis-2,4-dinitrophenylhydrazone mp 227–229° (aqueous dimethylformamide) [lit.[27] bp 125°; lit.[28] bis-2,4-dinitrophenylhydrazone mp 220.5–221.5° (aqueous dimethylformamide)]; nmr δ 2.28 (s, 3 H) and 1.24 (s, 9 H).

***erythro*-1-Phenyl-1,2-propanediol.** The compound was prepared from *trans*-phenylpropene in 54% yield by oxidation with *m*-chloroperbenzoic acid and hydration of the epoxide thus formed by aqueous $HClO_4$ in THF, using the procedure previously reported.[1] The pure compound was isolated as colorless powder: mp 89–91° (benzene–petroleum ether) [lit.[29] mp 91–92.5° (petroleum ether)]; nmr δ 7.27 (s, 5 H), 4.62 (d, J = 4 Hz, 1 H), 3.96 (m, 1 H), 2.80 (s, 2 H), and 1.01 (d, J = 6.2 Hz, 3 H). In a mixture with the threo isomer, the doublet at δ 4.62 was sufficiently well resolved to allow quantitation at 60 MHz.

***threo*-1-Phenyl-1,2-propanediol.** The compound was prepared in 22% yield by oxidation of *trans*-phenylpropene with magnesium sulfate–buffered potassium permanganate in aqueous ethanol, by the procedure previously reported.[1] Chromatography of the crude product on silica gel (5% ether in petroleum ether) gave the substantially pure diol which crystallized upon standing in benzene–petroleum ether: mp 51–53° [lit.[29] mp 52–54° (petroleum ether)]; nmr δ 7.27 (s, 5 H), 4.29 (d, J = 7.5 Hz, 1 H), 3.89 (m, 1 H), 3.58 (s, 2 H), 1.00 (d, J = 7 Hz, 3 H).

Hydride Reduction of Substrates. General Procedure. Into a dry, nitrogen-flushed test tube, containing a magnetic spin ball and fitted with a septum cap, was injected 1.5 mmol of hydride solution. After cooling to −78°, the substrate (0.5 mmol in 0.5 ml of the appropriate solvent) was added slowly with stirring. The mixture was stirred for 4 hr at −78°; the cold bath was then removed and stirring was continued at room temperature for 18–20 hr. The reaction was quenched by the cautious addition of 3 ml of water; sufficient 6 *N* HCl to dissolve the gelatinous precipitate was added, and the mixture was extracted with three 15-ml portions of ether. The combined extracts were dried, and the solvent was removed. The residue was heated briefly at reduced pressure to drive off volatile impurities; the product diol thus obtained was *ca.* 95% pure.

In reactions with protio hydride reagents, the diol was taken up in $CDCl_3$, and the solution was shaken with D_2O to preclude possible interference by the hydroxylic protons, prior to analysis by nmr. In reactions with the deuterated hydride reagents, the diol was subjected to cleavage with sodium metaperiodate, as described below.

Periodate Cleavage of α-Diols. General Procedure. The α-diol (50–75 mg) was dissolved in 5 ml of THF. To the stirred solution, at room temperature, was added sodium metaperiodate (500 mg) and then 3 ml of water. The flask warmed immediately and a voluminous precipitate of sodium iodate was noted within minutes. The flask was tightly stoppered, and the mixture was stirred for 3 hr. The reaction was quenched into saturated $NaHCO_3$, and the solution extracted with three portions of ether. The combined ether extracts were treated with 15 ml of methanolic 2,4-dinitrophenylhydrazine reagent and were set aside while the ether was allowed to evaporate slowly.

After the ether had evaporated, the precipitated 2,4-dinitrophenylhydrazone of hexanal or benzaldehyde was collected. With hexanal, water generally was added to the mixture to ensure quantitative precipitation of the derivative. The crude derivatives were recrystallized and dried *in vacuo* prior to analysis by isotope ratio mass spectrometry.

Meerwein–Ponndorf–Verley Reduction of α-Ketols. Representative Procedure. To a solution of DIBAH (5.0 ml of a 0.4 *M* toluene solution, 2.0 mmol), stirred at 0° under a nitrogen atomosphere, was added biacetyl (86 mg, 1.0 mmol) in 1.0 ml of toluene. The solution was stirred for 2 hr at room temperature (to allow reduction to the diol) and then was cooled to −78°. 2-Octanon-3-ol (144 mg, 1.0 mmol) dissolved in 1.0 ml of toluene was then added slowly. The cold bath was removed after 30 min and the mixture stirred for 24 hr at room temperature. The reaction was quenched with water; sufficient 1 *N* HCl was added to dissolve the gelatinous precipitate, and the products were isolated in ether. The ethereal solution of crude products was dried, concentrated to 10.0 ml, and analyzed by glpc at 145°. The per cent conversion was determined by external standardization with authentic diol mixture.

All MPV studies were done using the procedure above and the reagents, solvents and stoichiometries shown in Table III. Reactions with 1-phenyl-2-propanon-1-ol (5) were analyzed at 185°.

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Registry No.—TIBA, 100-99-2; DIBAH, 1191-15-7; $LiAlH_4$, 16853-85-3; $LiAl(OMe)_3H$, 12076-93-6; *erythro*-1-phenyl-1,2-propanediol, 1075-04-3; *threo*-1-phenyl-1,2-propanediol, 1075-05-4.

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