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Stereoselectivity in the Reduction of Aliphatic α-Ketols with Aluminum Hydride Reagents

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The reduction of six α-ketols with different patterns of substitution and size of substituents has been investigated using seven aluminum hydride reagents. The ratio of diastereomeric diols produced was determined by 220-MHz nmr analysis. In each case the predominant diol was the one predicted by Cram's cyclic model. The degree of stereoselectivity correlates well with α-ketol structure with only one reagent (triisobutylaluminum). With the other (agglomerated) reagents, selectivity is related only in an irregular manner to α-ketol structure.

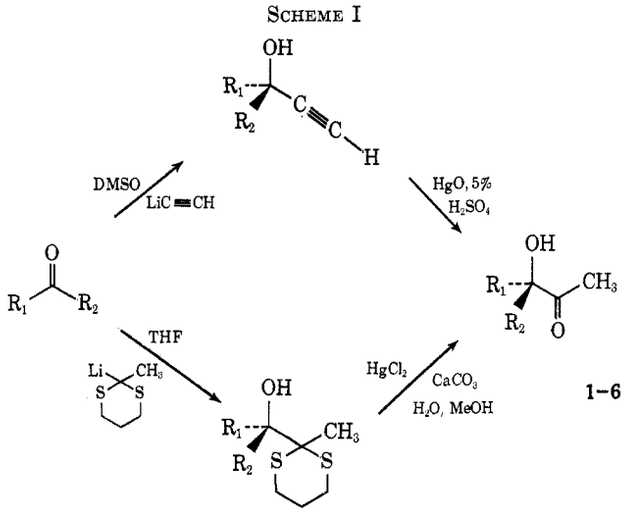
The stereoselective formation of olefins is a synthetic endeavor that has received considerable attention in recent years.[1] One of the approaches that has been successful in achieving complete stereospecificity is the conversion of 1,2-diols to the corresponding olefins, and a variety of methods for effecting this transformation has been reported.[2] Although the conversion of diol to olefin proceeds without loss of stereochemical integrity, the production of a single olefin isomer requires the availability of a single diastereomer of the precursor diol; hence, the problem of stereoselective olefin synthesis by this method is reduced to the problem of stereoselective diol synthesis.

Convenient precursors of diols are the related α-ketols. A number of recent synthetic methods have supplanted the classical acyloin condensation,[3] and permit the convenient synthesis of a wide variety of unsymmetrically substituted aliphatic α-ketols.[4] This report details the results of a study of the reductions of a number of di- and trisubstituted α-ketols using several aluminum hydride reagents with differing reduction properties.[5,6] As the resulting diols can be converted into olefins or epoxides, this work constitutes in a formal sense a stereoselective route to both of these systems.

Results

Synthesis of α-Ketols.—The α-ketols utilized in this study were prepared either by the mercuric ion catalyzed hydration of propargylic alcohols[4c] or by addition of 2-lithio-2-methyl-1,3-dithiane to carbonyl compounds, followed by mercuric ion assisted hydrolysis of the dithioketal[4a] (Scheme I). Yields, physical con-

SCHEME I



(1) For reviews see D. J. Faulkner, *Synthesis*, 175 (1971), and J. Reucroft and P. G. Sammes, *Quart. Rev., Chem. Soc.*, **25**, 135 (1971).

(2) E. J. Corey and R. A. E. Winter, *J. Amer. Chem. Soc.*, **85**, 2677 (1963); E. J. Corey, F. A. Carey, and R. A. E. Winter, *ibid.*, **87**, 934 (1965); F. W. Eastwood, K. J. Harrington, J. S. Josan, and J. L. Pura, *Tetrahedron Lett.*, 5223 (1970); J. N. Hines, M. J. Peagram, G. H. Whitman, and M. Wright, *Chem. Commun.*, 1593 (1968); G. Crank and F. W. Eastwood, *Aust. J. Chem.*, **17**, 1392 (1964); J. S. Josan and F. W. Eastwood, *ibid.*, **21**, 2013 (1968); J. F. McGhie, W. A. Ross, D. H. Laney, and J. M. Barker, *J. Chem. Soc. C*, 1 (1968).

(3) S. M. McElvain, *Org. React.*, **4**, 256 (1948).

(4) (a) D. Seebach, *Synthesis*, 17 (1969); (b) H. M. Walborsky, W. H. Morrison, and G. E. Niznik, *J. Amer. Chem. Soc.*, **92**, 6675 (1970); (c) M. Miocque, N. M. Hung, and V. Q. Yen, *Ann. Chim. (Paris)*, [13] **8**, 157 (1963); (d) T. Cohen and T. Tsuji, *J. Org. Chem.*, **26**, 1681 (1961); (e) S. Hoff, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **87**, 1179 (1968); (f) S.-O. Lawesson and S. Gronwall, *Acta Chem. Scand.*, **14**, 1445 (1960).

(5) Asymmetric induction in additions to aliphatic α-ketols has been studied extensively, but reactions involving attack by an organometallic (as opposed to a hydride) have received the closest scrutiny. For reviews see (a) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Engelwood Cliffs, N. J., 1971, Chapter 3; (b) S.-I. Yamada and K. Koga in "Selective Organic Transformations," Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1970, p 5 ff.

(6) Investigations which have examined the reduction of acyloins or their derivatives are (a) J. H. Stocker, P. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *J. Amer. Chem. Soc.*, **82**, 3913 (1960); (b) S. Yamada and K. Koga, *Tetrahedron Lett.*, 1711 (1967); (c) D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, **74**, 5828 (1952).

TABLE I

α-KETOLS. YIELDS AND PHYSICAL AND SPECTROSCOPIC PROPERTIES[a]

Compd	Substituent[b] R1	R2	Method[c]	Yield,[d] %	Bp, °C (mm)	Nmr[e] chemical shift, δ (multiplicity,[f] J, Hz) CH3	OH	R1	R2
1	n-C_5H_{11}	H	A	84	42 (0.17)	2.01 (s)	3.9 (u)	0.62 (t) 1.2 (u)	3.9 (u)
2	i-Pr	H	A	17		2.20 (s)	3.30 (s)	0.77 (d, 6.5)	4.06 (d, 2.5)
			B	24	68–72 (17)[g]			1.11 (d, 6.5) 2.20 (m)	
3	t-Bu	H	A	54	31–33 (0.25)[h]	2.20 (s)	3.35 (s)	1.0 (s)	3.76 (s)
4	Ph	CH_3	A	54	133 (10)[i]	2.07 (s)	4.1 (s)	7.2–7.5 (m)	1.74 (s)
5	i-Pr	CH_3	A	34		2.20 (s)	3.5 (s)	0.75 (d, 8.0)	1.30 (s)
			B	49	66–68 (10)			1.02 (d, 8.0) 1.97 (m)	
6	t-Bu	CH_3	B	31	178–180 (760)	2.18 (s)	3.5 (s)	0.92 (s)	1.20 (s)

[a] Satisfactory analytical data (± 0.4%) were obtained for all compounds and were made available to the Editor and referees. Compounds 2, 3, and 4 were analyzed as their semicarbazone derivatives. [b] Substitution per Scheme I. [c] A, *via* dithiane; B, *via* propargylic alcohol. [d] Isolated yield of pure α-ketol, based on starting carbonyl component. [e] 60 MHz, CCl_4 solution. [f] u = unresolved. [g] Semicarbazone mp 221–223° (methanol). [h] Semicarbazone mp 194–197° (aqueous ethanol). [i] Semicarbazone mp 182.5–184° (methanol).

TABLE II

PHYSICAL AND SPECTROSCOPIC PROPERTIES OF DIASTEREOMERIC DIOLS[a]

Compd	Substituent R1	R2	Configuration	Mp, °C	Nmr[b] chemical shift, δ (coupling, J, Hz) CH3	H	R1	R2
7	n-C_5H_{11}	H	erythro	42.5–44	1.13 (6.2)	*3.76* (6.2, 1.5)	*c*	3.58 (u)[d]
			threo	Liquid	1.18 (5.8)	3.58 (u)	*c*	*3.30* (u)
8	i-Pr	H	erythro	43.5–45.5	1.17 (6.3)	*3.88* (u)	0.85, 0.98 (6.0)[e]	*3.24* (3.5)
			threo	54–56	1.20 (6.0)	*3.76* (6.0)	0.88, 1.00 (4.0)[e]	*3.10* (u)
9	t-Bu	H	erythro	70–72	1.20 (6.4)	3.88 (6.2, 2.8)	0.96	*3.36* (u)
			threo	80.5–81.5	1.24 (6.4)	3.92 (6.4, 1.7)	0.94	*2.95* (1.7)
10	Ph	CH_3	erythro	Liquid	*0.90* (6.3)[f]	4.78 (6.3)	7.22	*1.50*
			threo	Liquid	*1.08* (6.3)[f]	4.78 (6.3)	7.22	*1.43*
11	i-Pr	CH_3	erythro	Liquid	1.19 (6.3)	3.59 (6.3)	*0.83, 0.98* (6.6)[e]	*1.11*
			threo	44–46	1.15 (6.0)	3.77 (6.0)	*0.93* (6.0)[e]	*1.02*
12	t-Bu	CH_3	erythro	96–97	1.26 (6.5)	3.95 (6.5)	*1.02*	*1.14*
			threo	22–24	1.21 (6.4)	3.80 (6.4)	*0.98*	*1.08*

[a] Satisfactory analytical data (±0.4%) were obtained for all compounds and were made available to the Editor and referees. [b] 220 MHz, $CDCl_3$ or CCl_4 solution. Signals used for quantitative analysis are italicized. [c] Multiple resonances 0.8–1.7 ppm. [d] u = unresolved. [e] Isopropyl methyl resonances. [f] 60 MHz.

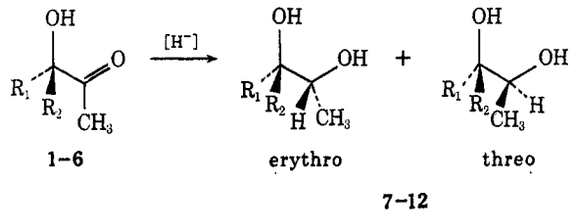
stants, and spectroscopic data for these compounds are shown in Table I.

While the propargylic alcohol route is better suited to large-scale preparations, the dithiane route was preferred as it gives a cleaner reaction. However, with the more severely hindered ketones, only the propargylic route gave satisfactory yields.

Identification of the Predominant Diastereomeric Diols.—Diastereomeric α-diols are generally distinguishable by nmr. Anet[7] has correlated the coupling constants of butane-2,3-diol acetonides; more recently Nakanishi, *et al.*,[8] have developed a method which utilizes the differences in NOE and W-type coupling to distinguish between diastereomers of α-diols and certain of their derivatives. While these methods are laudable in their general applicability for the identification of pure α-diols, they are ill-suited to the analysis of mixtures of diastereomers. Therefore, we have applied the observations of Anet[7] and Cavill[9] of the differing chemical shifts of substituents on the diastereomeric carbons in analyzing the mixtures formed in the reduction reactions (Scheme II). These regions of nonequivalence and potential analytical utility are summarized in Table II.

(7) F. A. L. Anet, *J. Amer. Chem. Soc.*, **84**, 747 (1962).
(8) K. Nakanishi, D. A. Schooley, M. Koreeda, and I. Miura, *ibid.*, **94**, 2865 (1972).
(9) G. W. K. Cavill, D. G. Laing, and P. J. Williams, *Aust. J. Chem.*, **22**, 2145 (1969).

SCHEME II



1–6 erythro threo

7–12

In making these assignments, we were guided by the assumption that Cram's "cyclic" model[10] would be applicable to the reductions giving the diols; *i.e.*, in all cases the erythro isomer would predominate (Scheme II). However, to establish the assignments unequivocally, we prepared authentic samples of the diols by stereospecific epoxidation of isomerically pure olefins with *m*-chloroperbenzoic acid, followed by hydration with 30% aqueous perchloric acid in tetrahydrofuran. This procedure gave the isomerically pure diols, except in the case of 2-phenylbutane-2,3-diol (**10**), which gave the same mixture of diols from either isomer of 2-phenyl-2-butene. Samples of the pure diastereomers of **10** were prepared by cis hydroxylation of the pure olefin isomers, using magnesium sulfate buffered potassium permanganate in aqueous ethanol. In all

(10) D. J. Cram and D. R. Wilson, *J. Amer. Chem. Soc.*, **85**, 1245 (1963), and references cited therein.

TABLE III

YIELD OF DIOL PRODUCTS AND PER CENT ERYTHRO DIASTEREOMER PRODUCED IN THE HYDRIDE REDUCTION OF α-KETOLS

	Reactant[a]		% Erythro[b] (diol yield %)[c]						
Compd	R_1	R_2	TIBA ($PhCH_3$)	DIBAH ($PhCH_3$)	$LiAlH_4$ (THF)	$LiAl(OMe)_3H$ (THF)	REDAL (PhH:$PhCH_3$)	AlH_3 (THF)	$LiAl(O\text{-}t\text{-}Bu)_3H$ (THF)
1	n-C_5H_{11}	H	54 (97)	68 (98)	70 (95)	78 (73)	62 (91)	71 (93)	63 (85)
2	i-Pr	H	83 (90)	62 (74)	73 (62)	66 (53)			
3	t-Bu	H	>95 (73)	73 (79)	75 (97)	77 (88)			
4	Ph	CH_3	82 (62)	78 (79)	67 (86)	57 (85)			
5	i-Pr	CH_3	85 (72)	71 (89)	49 (87)	60 (86)			
6	t-Bu	CH_3	91 (73)	60 (85)	64 (87)	70 (90)			

[a] All reductions were conducted in the solvent indicated using a threefold molar excess of hydride reagent, for 4 hr at −78° with gradual warming to 25°. [b] Determined by 220-MHz nmr analysis, Table II. [c] Isolated yield.

cases, the nmr spectra of the authentic samples were in agreement with initial assignments based on Cram's cyclic model.

Quantitative Analysis of Mixtures of Diastereomeric Diols.—In our initial efforts to quantitate the ratio of diol products we utilized gas chromatographic analysis; however, the only phases capable of separating the diastereomeric diols gave poorly reproducible chromatograms. Furthermore, the diols were subject to extensive decomposition on the column.

It was found that 220-MHz nmr provided sufficient resolution to obtain meaningful integration data of selected signals in each mixture (Table II). Repetitive integration of these signals and, where possible, comparison of integrals of alternative signals as internal checks, gave average deviations of ±2%. Duplicate experiments performed in all cases gave results which were within these limits, except $LiAl(OMe)_3H$. In the case of $LiAl(OMe)_3H$, a larger variation (±6%) was found and was ascribed primarily to differences in the constitution of the reagent, which was prepared *in situ* immediately prior to addition of the substrate.

Reduction of α-Ketols.—The reducing agents utilized in this study were all of the aluminum hydride type. Lithium aluminum hydride ($LiAlH_4$), aluminum hydride (AlH_3), lithium trimethoxyaluminum hydride [$LiAl(OMe)_3H$], and lithium tri-*tert*-butoxyaluminum hydride [$LiAl(O\text{-}t\text{-}Bu)_3H$] reductions were conducted in tetrahydrofuran (THF) as solvent; triisobutylaluminum (TIBA) and diisobutylaluminum hydride (DIBAH) reactions were run in toluene, and sodium bis(2-methoxyethoxy)aluminum hydride (RED-AL)[11] in benzene–toluene (1:1). Reduction of all six α-ketols by TIBA, DIBAH, $LiAlH_4$, and $LiAl(OMe)_3H$ was examined. Only the reaction of the least selective primary substituted system (**1**) was investigated with all seven reagents.

The reduction reaction proceeded cleanly in all cases to give the product diols in moderate (*ca.* 55%) to excellent (>95%) yields. The yield and ratios of diastereomeric diols formed are summarized in Table III, and the degree of stereoselectivity in Table IV.

Discussion

Cram's cyclic model for steric control in asymmetric induction was devised to predict the diastereomer that would predominate in the reaction of a nucleophile with a chiral ketone containing a group on the α carbon that is capable of complexing with the counterion of the reagent. The α-ketols we have studied, therefore, fall in the predictive domain of this model, and our results do indeed conform to the model's predictions to the extent that, in each example studied, the diastereomer that predominates (within experimental error) is the anticipated erythro isomer.

(11) Trademark of The Aldrich Chemical Co., Milwaukee, Wis.

TABLE IV

STEREOSELECTIVITY OBSERVED IN α-KETOL REDUCTIONS

	Reactant		Stereoselectivity (diastereomer ratio)[a]			
Compd	R_1	R_2	TIBA	DIBAH	$LiAlH_4$	$LiAl(OMe)_3H$
1	n-C_5H_{11}	H	8 (1.17)	36 (2.13)	40 (2.33)	56 (3.55)
2	i-Pr	H	66 (4.88)	24 (1.63)	46 (2.70)	32 (1.94)
3	t-Bu	H	>90 (19)	46 (2.70)	50 (3.00)	54 (3.35)
4	Ph	CH_3	64 (4.56)	56 (3.55)	34 (2.03)	14 (1.33)
5	i-Pr	CH_3	70 (5.67)	42 (2.45)	−2 (0.96)	20 (1.50)
6	t-Bu	CH_3	82 (10.11)	20 (1.50)	28 (1.78)	40 (2.33)

[a] Data is taken from Table III and recast in form more suitable for comparison of stereoselectivities. Selectivity = % erythro − % threo (if >0, implies that cyclic model holds); diastereomer ratio is % erythro/% threo (if >1, implies that cyclic model holds).

The three models for asymmetric induction (open chain,[6c] dipolar,[12] and cyclic[6c]) were originally presented as means for predicting only which diastereomeric product would predominate in an addition to a chiral ketone, and not the degree to which it would predominate (stereoselectivity). Recently, Karabatsos[13] and Felkin[14] have attempted to extend the open-chain and dipolar models so that some correlation could be made between changes in ketone structure and the resulting changes in stereoselectivity of the addition. Substantially modified transition-state models have emerged from these two studies.

If one attempts to extend the cyclic model in a similar fashion, it is clear that the simple picture of the cyclic model with its attendant controlling interactions between the attacking reagent with R_S and R_L (Scheme III) cannot provide an adequate correlation for our data (*vide infra*). Indeed, Morrison and Mosher[15] have cautioned that, of the three models for asymmetric induction, the systems covered by the cyclic model are those most subject to alterations in stereoselectivity with change of solvent, reagent, and bulk associated with the metal–carbonyl complex. In some cases, the selectivity observed has even been the reverse of that predicted by the cyclic model;[5a,6a,10,16] discrepancies of this magnitude are only infrequently encountered with the open-chain and dipolar models.[15]

(12) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959).

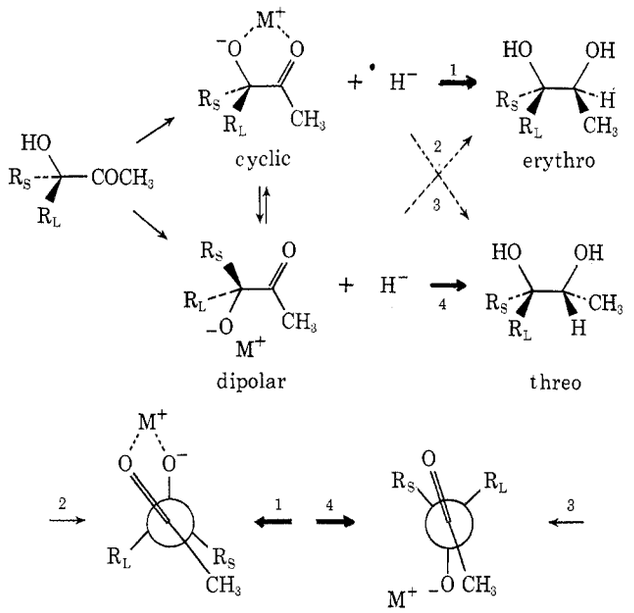
(13) G. J. Karabatsos, *J. Amer. Chem. Soc.*, **89**, 1367 (1967).

(14) M. Chérest, H. Felkin, and N. Pruduct, *Tetrahedron Lett.*, 2201 (1968).

(15) Reference 5a, pp 97 and 113.

(16) J. H. Stocker, *J. Amer. Chem. Soc.*, **88**, 2878 (1964).

SCHEME III



In order to rationalize the unreliability of the cyclic model, it has been proposed[10] that, in certain "cyclic model" systems, addition may actually be taking place *via* two competing transition states, the cyclic and the dipolar (Scheme III). As in each case the dipolar model predicts predominance of the diastereomer opposite to that of cyclic model, reversal of the stereochemical course of the reaction may be ascribed to a change in the partitioning of the reaction between the two transition states. If it is indeed true that so many courses of reaction are in competition, then prediction of the effect of alterations in reactant structure, solvent, and nature of reagent on reaction stereoselectivity becomes laden with ambiguity. However, there are a number of results from our study in which the relationship between stereoselectivity and reagent and reactant structure is worthy of discussion.

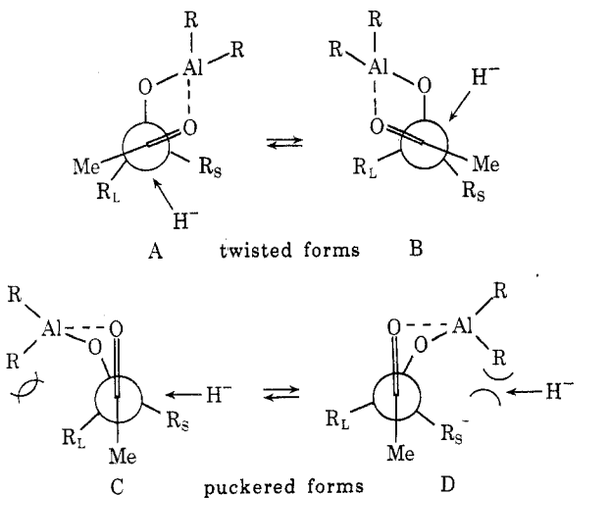
Aggregation of Reducing Reagent.—In his early work on the addition of organolithium reagents to α-ketols, Cram[10] noted that the stereoselectivity decreased with change of solvent from ether to pentane. He suggested that the increased agglomeration of the lithium reagent in the hydrocarbon solvent, with the attendant increase in steric bulk associated with the metal alkoxide–carbonyl complex, might allow a portion of the reaction to proceed *via* the less encumbered dipolar transition state. More recently, Ashby[17] has noted the concentration dependence of stereoselectivity in the hydride reduction of 2-methylcyclohexanone, and has ascribed these variations to changes in reagent aggregation; the stereoselectivity of reduction by $LiAl(OMe)_3H$ is most sensitive to change in the concentration range in which association of the reagent is changing most rapidly. Conversely, the stereoselectivity of reduction by $LiAl(O\text{-}t\text{-}Bu)_3H$, which is monomeric over the range investigated, is essentially concentration independent.

A comparison of our results with TIBA and DIBAH provides a striking example of this effect, especially in the case of disubstituted α-ketols. Thus, the reduction with TIBA, reported to be monomeric in solution,[18] is highly sensitive to changes in the steric requirements of the substituents on the α-ketol, and stereoselectivity changes in a regular manner consistent with the cyclic model. On the other hand, reaction with DIBAH, a considerably bulkier trimer[18,19] [as well as the agglomerated $LiAlH_4$ and $LiAl(OMe)_3H$],[17] displays neither regular nor marked increase in selectivity with increase in the bulk of R_L.

Nature of the Alkoxide–Carbonyl Complex.—In view of our results as discussed above, as well as those previously obtained by other workers, it is tempting to conclude that competition between the sterically more compressed cyclic model and the freer dipolar model is primarily dependent upon the state of aggregation of the reducing agent, and that it is this competition which determines the observed stereoselectivities of the reaction. It is disturbing, however, that in at least two cases we have studied (DIBAH and $LiAlH_4$) the change in selectivity is related in an irregular manner to the change in bulk of R_L *vs.* R_S. Alternative explanations for these observations may be that, in addition to reagent aggregation, (a) the steric bulk of R_L may also be of importance in creating an effective partitioning among cyclic, dipolar, and certain open-chain transition states (Scheme III) or that (b) the cyclic transition state predominates in all cases but is subject to conformational changes. More detailed analysis of hypothesis a is difficult, but hypothesis b deserves further comment.

If it is assumed that the chelated ring is planar and rigid, then the only effects that direct the stereochemical course of the reduction are the interactions between the attacking hydride reagent with R_L and R_S. Stocker[6a] has speculated that, in certain cases where neither the acyclic model nor a competing cyclic dipolar model provides an adequate explanation, a twisting of the five-membered ring (Scheme IV, A and

SCHEME IV



B) may be taking place. It should be noted that, in addition to possible relief of steric compression, such torsion would also allow a small decrease in dipolar in-

(17) E. C. Ashby, J. P. Sevenair, and F. R. Dobbs, *J. Org. Chem.*, **36**, 197 (1971).

(18) E. G. Hoffman, *Justus Liebigs Ann. Chem.*, **629**, 104 (1960); K. Ziegler, W. R. Kroll, W. Larbigand, and O. W. Steudle, *ibid.*, **629**, 53 (1960).

(19) H. W. Schroetter and E. G. Hoffman, *Ber. Bunsenges. Phys. Chem.*, **68**, 627 (1964).

teractions. Alternatively, conformational deformation may take the form of ring puckering (Scheme IV, C and D).

Either of these conformational models might suffice to explain an irregular dependence of stereoselectivity upon alteration in the relative sizes of R_L and R_S. For instance, in the twisted species A and B, increase in the size of R_L relative to R_S should favor attack by hydride from the side of R_S (bottom right), but at the same time this change would shift the conformational equilibrium in favor of species B to minimize the eclipsing interaction between Me and R_L; attack on the same carbonyl face in B, however, is now hindered by interactions between entering hydride ion and the bulky aluminum alkoxide–carbonyl chelate. Similarly, in the puckered species C and D, increase in the size of R_L relative to R_S makes interactions between hydride and R_S more favorable to attack from the side of R_S (right), but at the same time the increased interaction between the chelating metal and its ligands with R_L tend to favor the species D, in which attack from the right is subject to unfavorable interactions between entering hydride and the aluminum species.

Anomalous Behavior of a Phenyl Substituent.—With two reagents [TIBA and $LiAl(OMe)_3H$] the stereoselectivity observed in the reduction of the phenyl-substituted α-ketol **4** is less than that obtained in the analogous isopropyl-substituted case (**5**), and, with two reagents (DIBAH and $LiAlH_4$), the reduction is more selective than in the corresponding *tert*-butyl case (**6**). In numerous examples that follow Cram's open-chain model, a phenyl substituent is always rated as being greater in steric bulk than an isopropyl group, and is generally considered comparable to or even larger than a *tert*-butyl group.[20] In this connection, the alteration in selectivity in the reduction of the α-phenyl α-ketol is curious; it is possible that this case reflects mediation of effects other than the simple steric arguments discussed above.

Conclusions.—The stereoselectivities obtained in the hydride reduction of α-ketols do not appear to follow a generally regular pattern, other than that the predominant diastereomer formed is that predicted by Cram's cyclic model for asymmetric induction. In the case of a monomeric reagent (TIBA), the degree of stereoselectivity does correlate well with changes in the relative steric bulk of the substituents on the α carbon, but, with agglomerated reagents, selectivity changes in an irregular manner. It is perhaps safe only to say that the highest selectivities are not necessarily associated with the most hindered α-ketols or aggregated hydride donors, nor the lowest selectivities with the least hindered, but that each reagent retains a selectivity peculiar to the specific system with which one is working.

Experimental Section

General.—Melting points were determined on a Fisher-Johns apparatus, and are uncorrected. Nuclear magnetic resonance spectra were determined in CCl_4 or $CDCl_3$ solution on Varian A-60 or HR-220 spectrometers; chemical shifts are reported in parts per million downfield from internal tetramethylsilane (δ scale). Elemental analyses were performed by the microanalytical service of the University of Illinois.

(20) Reference 5a, p 89.

Glassware for reactions involving organometallic reagents was dried for a minimum of 3 hr at 120°. Solvents for these reactions were dried by distillation from appropriate reagents. All other reagents were used as supplied, unless otherwise noted. Solutions were dried over $MgSO_4$ unless otherwise noted.

Isomerically pure olefins used in the preparation of standard diols were obtained from Aldrich Chemical Co. or Chemical Samples Co. Lithium aluminum hydride was obtained from Ventron Corp. THF solutions of this reagent, aluminum hydride, and lithium trimethoxyaluminum hydride were prepared by the method of Brown.[21] THF solutions of lithium tri-*tert*-butoxyaluminum hydride were prepared from the pure material obtained from Aldrich Chemical Co. Sodium bis(methoxyethoxy)aluminum dihydride (RED-AL, 70% in benzene, Aldrich) was diluted with benzene–toluene (1:1) prior to use. Toluene solutions of triisobutylaluminum (TIBA) and diisobutylaluminum hydride (DIBAH) were prepared from the neat liquids as supplied by Ventron Corp.

All of the above solutions were assayed for available hydride by gas titration immediately prior to use.

3-Hydroxy-2-alkanones.—A series of 3- and 4-substituted 3-hydroxy-2-alkanones was prepared; yields, physical properties, and nmr data for these compounds are summarized in Table I. The procedure given below for the preparation of 3,4-dimethyl-2-pentanon-3-ol (**5**) was generally used in the preparation of other members of the series, as indicated in the Method column of Table I.

Method A. *Via* **1,3-Dithiane Mercaptal.**—To 2-methyl-1,3-dithiane (1.34 g, 10 mmol), dissolved in *ca.* 60 ml of THF and stirred at −20° under a nitrogen atmosphere, was added an equivalent amount of *n*-butyllithium (1.23 *M*, in pentane). The mixture was stirred at −20° for 5 hr, the temperature was then reduced to −78°, and 3-methyl-2-butanone (0.86 g, 10 mmol) in 10 ml of THF was added over a period of 30 min. After an additional 30 min, the cold bath was removed and the solution was stirred at room temperature for several hours. The solution was poured onto 300 ml of ice and water, and extracted three times with chloroform. The organic extracts were washed twice with 10% KOH (0°), once with water, and dried (K_2CO_3), and the solvent was removed by flash evaporation.

A vigorously stirred solution of the crude dithiane in 100 ml of 80% aqueous methanol was treated with $CaCO_3$ (1.0 g, 10 mmol) and $HgCl_2$ (5.44 g, 20 mmol). After refluxing for 5 hr the mixture was cooled and filtered, and the methanol was removed by flash evaporation. The residue was diluted with brine and extracted with three portions of ether. The combined ether extracts were washed with water, saturated aqueous ammonium chloride, and again with water, and then dried. Evaporation of the solvent and distillation gave 0.44 g (34%) of the product, bp 65–69° (10 mm).

Method B. *Via* **Propargylic Alcohol.**—3-Methyl-2-butanone (8.6 g, 0.10 mol) dissolved in 20 ml of DMSO was added over a period of 45 min to a slurry of lithium acetylide–ethylenediamine complex (6.4 g, 0.2 mol) in 30 ml of DMSO, stirred at 0° under a nitrogen atmosphere. After 1 hr the ice bath was removed and the mixture was stirred for 12 hr. The mixture was slowly poured into *ca.* 900 ml of ice water, which was then continuously extracted with ether. The extract was dried and the solvent was removed by distillation.

The crude propynol was added over a period of 1.5 hr to a stirred solution, heated to 60°, of 100 ml of 5% H_2SO_4 in which 2.5 g of HgO (red) had been dissolved. After the addition was complete the mixture was heated for an additional 1 hr, cooled, and filtered. The filtrate was extracted three times with ether, the combined extracts were dried, and the solvent was removed by flash evaporation. Two distillations of the oily residue afforded 6.4 g (49%) of the product, bp 66–68° (10 mm).

Preparation of Authentic Samples of Diols. Trans Hydroxylation.—To a solution of *m*-chloroperbenzoic acid (5.1 g of 85% technical material, 25 mmol) in *ca.* 150 ml of methylene chloride was added over a period of 30 min 20 mmol of the olefin. The solution was stirred for 20–24 hr and then quenched by the addition of 10 ml of saturated Na_2SO_3. The mixture was diluted with saturated bicarbonate, and the layers were separated. The organic layer and two ether extracts of the aqueous layer were dried and the solvent was evaporated.

(21) H. C. Brown and P. M. Weissman, *J. Amer. Chem. Soc.*, **87**, 5614 (1965); H. C. Brown and N. M. Yoon, **88**, 1464 (1966).

The crude product was dissolved in 150 ml of THF and treated with 50 ml of 30% $HClO_4$. After stirring for 8 hr, the solution was neutralized with 10% NaOH, diluted with brine, and extracted twice with ether. The combined ether extracts were dried and the solvent was evaporated. Liquid products were purified by bulb-to-bulb distillation; solids were recrystallized from hexane or benzene–hexane solution.

Cis Hydroxylation.[22]—To 20 mmol of the olefin, dissolved in *ca.* 100 ml of ethanol and stirred at −20°, was added over a period of 20 min a solution of potassium permanganate (2.12 g, 13.4 mmol) and magnesium sulfate (1.5 g, 12.5 mmol) in *ca.* 200 ml of water. The mixture was immediately filtered through Celite, and the cake was washed with methanol and ether. The filtrate was concentrated, diluted with brine, and extracted several times with ether. The combined extracts were dried and the solvent was evaporated. Chromatography on silica gel (5% ether in hexane) gave the substantially pure diol, which was distilled (bulb to bulb) or recrystallized as necessary.

Physical constants and selected nmr data for compounds prepared by these methods are summarized in Table II. Nmr signals not given in Table II were fully consistent with the assigned structures.

Hydride Reduction of α-Ketols. 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 ketol (0.5 mmol in 0.5 ml of toluene) was added slowly with stirring. After 4 hr, the cold bath was removed and stirring was continued at room temperature for 18 to 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 three times with 15-ml portions of ether. The combined extracts were dried and the solvent was evaporated. The residue was heated briefly under vacuum to drive off any unreacted ketol; the product diol thus obtained was *ca.* 95% pure.

(22) M. F. Clarke and L. N. Owen, *J. Chem. Soc.*, 315 (1949).

Registry No.—**1**, 37160-77-3; **2**, 6986-70-5; **3**, 7737-47-5; **4**, 3155-01-9; **5**, 37160-81-9; **6**, 6196-59-4; *erythro*-**7**, 37163-97-6; *threo*-**7**, 37163-98-7; *erythro*-**8**, 6702-10-9; *threo*-**8**, 6464-40-0; *erythro*-**9**, 23646-57-3; *threo*-**9**, 23646-58-4; *erythro*-**10**, 37164-02-6; *threo*-**10**, 37164-03-7; *erythro*-**11**, 37164-04-8; *threo*-**11**, 37164-05-9; *erythro*-**12**, 37164-06-0; *threo*-**12**, 37164-07-1; TIBA, 100-99-2; DIBAH, 1191-15-7; $LiAlH_4$, 16853-85-3; $LiAl(OMe)_3H$, 12076-93-6; REDAL, 21608-56-0; AlH_3, 7784-21-6; $LiAl(t\text{-}AuO)_3H$, 17476-04-9.

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Stereochemistry of the Diels–Alder Reaction. V. Fluorinated Trans-Olefinic Acids and Derivatives with Cyclopentadiene

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The Diels–Alder reactions of a series of fluorinated *trans*-crotonic acids, esters, amides, an acid chloride, and an aldehyde with cyclopentadiene at 25° are discussed. The endo–exo ratios were determined by gas chromatographic and/or infrared analyses. The fluoroalkyl groups in all cases dominated the stereochemical course of the reactions, and in one series of crotonic acids the endo–exo ratios correlated very well with the inductive effects (σ_I) of these groups.

Two of the previous papers[1,2] in this series dealt with the Diels–Alder reactions of *trans*-4,4,4-trifluorocrotonic acid with various dienes. A third paper[3] examined the stereochemistry of the reaction of cyclopentadiene with several other *trans*-β-perfluoroalkylcrotonic acids. Olefins with fluorines in varying numbers and positions have also been studied with cyclopentadiene, butadiene, and anthracene.[4,5] In this paper we describe the stereochemistry of the products from the reactions of cyclopentadiene with a series of *trans*-β-fluoroalkyl-α,β-unsaturated acids, amides, esters, etc.

A list of dienophiles that were prepared for this study is given in Table I. The acids were prepared *via* hydrolysis of the corresponding esters, which in turn were prepared by means of the Knoevenagel reaction as generally described in previous papers.[6] Only one ester, ethyl 4-fluorocrotonate (**3**), was prepared differently owing to the fact that 2-fluoroethanal is relatively inaccessible. Numerous attempts to fluorinate methyl and ethyl 4-bromocrotonate using sodium, potassium, lithium, and silver fluorides under various conditions afforded only 7.5% of **3** as the best yield.[7]

All the dienophiles were assigned the trans configuration mainly on the basis of infrared absorption at *ca.* 5.95 and 10.30 μ, which is diagnostic for a trans system.[8] Proton magnetic resonance spectra for these compounds were very complex due to ^1H–^{19}F coupling.

Diels–Alder Reactions.—The dienophiles listed in Table I were stirred for 16–18 hr with a slight excess of cyclopentadiene at 25° in a constant-temperature

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(1) E. T. McBee, C. G. Hsu, and C. W. Roberts, *J. Amer. Chem. Soc.*, **78**, 3389 (1956).

(2) E. T. McBee, C. W. Roberts, and C. G. Hsu, *ibid.*, **78**, 3393 (1956).

(3) H. P. Braendlin, A. Z. Zielinski, and E. T. McBee, *ibid.*, **84**, 2109 (1962).

(4) H. P. Braendlin, G. A. Grindahl, Y. S. Kim, and E. T. McBee, *ibid.*, **84**, 2112 (1962).

(5) E. T. McBee, C. G. Hsu, O. R. Pierce, and C. W. Roberts, *ibid.*, **77**, 915 (1955).

(6) (a) E. T. McBee, Y. S. Kim, and H. B. Braendlin, *ibid.*, **84**, 3154 (1962); (b) A. Z. Zielinski, E. T. McBee, and H. P. Braendlin, *Rocz. Chem.*, **37**, 905 (1963).

(7) (a) D. R. Bennett, K. S. Andersen, M. V. Anderson, Jr., D. N. Robertson, and M. B. Chenoweth, *J. Pharmacol. Exp. Ther.*, **122**, 489 (1958). (b) A 16% yield of ethyl 4-fluorocrotonate was obtained from 1-chloro-3-fluoropropan-2-ol by E. D. Bergmann, S. Cohen, and I. Shahak, *J. Chem. Soc.*, 3448 (1961). See also F. L. Pattison and B. C. Saunders, *J. Chem. Soc.*, 2745 (1949).

(8) (a) L. F. Hatch and S. S. Nesbitt, *J. Amer. Chem. Soc.*, **72**, 727 (1950); (b) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1956.