Stereodependence of the Effect of α Substituents on the Face Reactivity of Conformationally Rigid Ketones toward Metal Hydrides. Is There an Antiperiplanar (Cieplak) Effect?

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The relative rates of hydride addition to the carbonyl group of the conformationally fixed bridged biaryl ketone, **1**, and its α derivatives bearing methyl, methylthio, methoxy, chloro, and fluoro substituents in axial-like and equatorial-like orientations have been measured for three different reactions. The derived rate constants were partitioned, on the basis of diastereoselectivity, to provide reactivities for each face *antiperiplanar* to the axial substituents and *anticlinal* to the equatorial substituents. These *face reactivities* gave reasonably linear correlations with the inductive substituent parameter, σ_I. The strength of the inductive effects as indicated by the slopes of the Taft plots were large and positive, small and positive, and negative for the reductions involving lithium aluminum hydride, sodium borohydride, and triethylsilane, respectively. The substituent effects on face reactivity and their stereodependencies failed to follow either the theory of Cieplak or that of Anh. The major influences of substituents can be explained on the basis of through-bond interactions with the transition state and the differences between axial and equatorial effects on electrostatic (through-space) interactions with the transition state.

The preferred course of addition of a nucleophile to the carbonyl group of acyclic aldehydes and ketones was the subject of the pioneering studies of Cram and co-workers.[1] A resultant rule, Cram's rule, predicted the major product of the addition to a carbonyl group with an adjacent chiral center, a process now commonly referred to as π-facial diastereoselectivity.[2] In another nucleophilic addition, that of hydride to cyclohexanones, the product normally observed was the result of preferred axial attack. Further studies on the stereochemical course of both addition reactions gradually led to an integrated explanation, the Felkin−Anh theory.[3,4] In this theory, the π-facial diastereoselection for axial attack on cyclohexanones was attributed (by Felkin) to lesser torsional interactions in the transition state and to an additional favorable orbital interaction between the incipient nucleophile-to-carbon bond as donor for the acyclic cases (by Anh) and the C−C bond *antiperiplanar (app)* to it as acceptor. A few years later Cieplak[5] put forward a novel alternative theory in which the preference for axial attack could be explained on the basis of a dominant orbital interaction related to that of Anh but involving the C−H bond as donor to the bond being formed with the attacking (*app*) nucleophile. Cieplak proposed an order for the size of this orbital interaction to be C−H > C−C > C−Cl which was the reverse of an earlier prediction of Anh. His theory of orbital interaction, now referred to as the "Cieplak effect" was thoroughly documented with rational arguments for it being the major factor responsible for axial attack.[5]

Early experimental evidence in support of his theory came from the extensive contributions of le Noble[6] who chose the rigid adamantan-2-one skeleton for determination of the effects of electronegative substituents at C-5 on the face selectivity for nucleophilic additions at C-2. An extensive study of a variety of nucleophilic additions to a series of 3-substituted cyclohexanones by Cieplak, Tait, and Johnson[7] provided additional support. A thorough analysis of the correlations of face selectivity (log k_{ax}/k_{eq}) versus the inductive substituent parameter σ_I led these authors to conclude that the substituent exerted its effect by decreasing the C_2-C_3 bond donation to the incipient bond in the equatorial transition state in proportion to its substituent electron-withdrawing power.[7] This important paper elicited a huge response. Almost invariably, subsequent experiments investigated the effect of electronegative substituents on face selectivity in reactions (usually reductions) involving other cyclic ketones of known conformational bias or rigor. Figure 1 summarizes a number of these systems which includes cyclopentanones,[8] bicyclo[2.2.1]heptanones,[9] decalin-1-ones,[10] 5-aza- and 5,7-diazaadamantan-2-one,[11] and cyclohexa-2,5-dienones,[12] all bearing substituents in the β or more remote positions.

This approach has provided only limited information, specifically the face selectivity or rate ratio for attack at the face of the carbonyl *app* to the two C−H or to the two C−C bonds. With the assumption of topographical equivalence for the two faces of the structures A−E in Figure 1, interpretation of the face selectivities involved a choice between Cieplak's proposed nonclassical orbital

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(2) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; pp 37−39.
(3) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205.
(4) (a) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
(5) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.
(6) Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 199.
(7) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.
(8) (a) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 980. (b) Halterman, R. L.; McCarthy, B. A.; McEvoy, M. A. *J. Org. Chem.* **1992**, *57*, 5585.
(9) (a) Mehta, G.; Khan, F. A.; Gadre, S. R.; Shirsat, R. N.; Ganguly, B.; Chandrasekhar, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1390. (b) Mehta, G.; Khan, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 6140. (c) Mehta, G.; Khan, F. A. *Tetrahedron Lett.* **1992**, *33*, 3065. (d) Kumar, V. A.; Venkatesan, K.; Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *Tetrahedron Lett.* **1992**, *33*, 3069.

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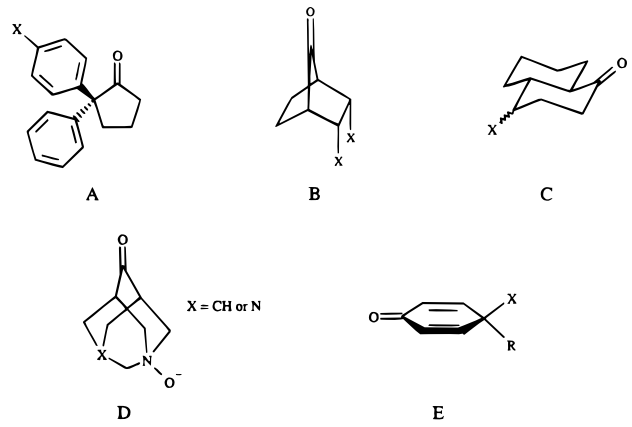

Figure 1. Representative examples of rigid carbocyclic ketones used for measurements of face selectivity in nucleophilic addition reactions.

interactions and Houk's well-documented electrostatic (through-space) inductive effects.[10,13] Only the latter could account for the influence of polar γ substituents on diastereoselectivity in reductions involving structures C and E.[12] A recent review[14] summarizes both the experimental and theoretical contributions to the controversy with comments on their conflicting interpretations.[15]

In spite of the above reservations, the Cieplak effect continues to be proposed as an important influence on stereoselectivity in several other commonly encountered reactions.[16] Such extensions serve to emphasize the importance of obtaining further evidence on the focal point of the controversy, the reason for preferred axial attack in the addition of hydride ion to cyclohexanones.

To complement the existing face selectivity data, information on the effect of substituents on the rate of hydride addition to the face *app* to it ought to be enlightening. Few such measurements of *face reactivities* have been described. In the first of these, Eliel and Senda[17] determined the effects of methyl substitution at carbons 3 and 4 of cyclohexanone on the rates of reduction relative to cyclohexanone. By consideration of the stereoselectivity for each reduction, they apportioned the relative rates to the two faces of the carbonyl, thus providing face reactivities. The effect of an α methyl group on the reactivity of cyclohexanone toward sodium borohyride (SBH) in 2-propanol was initially studied by Rickborn and Wuesthoff.[18] Later, such reductions of several conformationally fixed 2-methylcyclohexanones were reported by Wigfield and Phelps.[19] By assuming additive effects due to methyl substitution they estimated a small retarding effect (0.6 kcal/mol) for an equatorial methyl on equatorial (*anticlinal*) attack but no detectable influence of an axial methyl on axial (*app*) attack by hydride ion, i.e., the face reactivity (k^{app}/k_H) was found to be 1. The only other substituent effect on face reactivity, that of the methoxyl group, was measured by Senda and co-workers.[20] In the reduction of 2,4-*t*-dimethyl-*r*-2-methoxycyclohexanone by lithium aluminum hydride (LAH), they estimated[21] that the axial methoxyl caused a 25% decrease in the face reactivity toward *app* attack ($k^{app}/k_H = 0.75$).

To make a more extensive test of existing theories, we have undertaken a study of the reactivity of individual faces of the carbonyl group toward hydride ion as a function of both structure and stereochemistry of a variety of α substituents. Anh has predicted the order of stabilization of the transition state by an *antiperiplanar* α substituent to be C−H < C−C < C−Cl whereas Cieplak has proposed the opposite, C−S > C−H > C−C > C−Cl ≈ C−O. Specifically, we have measured the face reactivities in the addition of hydride ion to a series of ketones having the requisite α substituents (methyl, methylthio, methoxyl, and chloro as well as equatorial fluoro) oriented axially to accept *antiperiplanar* attack and, for comparison, equatorially to undergo *anticlinal* attack. To this end we have chosen as parent structure the bridged biaryl ketone **1**,[22] which offers two specific advantages over cyclohexanone as a model for studying conformational effects on reactivity.[23] While maintaining axial-like and equatorial-like bonds α to the carbonyl (see Figure 2), its seven-membered ring has a greater rigidity,[24] and has no available boat or other alternative conformation.

Preparation of α Derivatives of 1

Previously we have described the preparation and conformational properties[25] of the axial and equatorial methyl (**2**, **3**), chloro (**4**, **5**), and methoxy (**6**, **7**), derivatives

(10) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018. For an alternative consideration of electrostatic effects using a frontier molecular orbital approach, see: Huang, X. L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 4025, 6017.

(11) (a) Hahn, J. M.; le Noble, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1916. (b) Gonikberg, E. M.; le Noble, W. J. *J. Org. Chem.* **1995**, *60*, 7751.

(12) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678.

(13) Coxon, J. M; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418.

(14) Gung, B. W. *Tetrahedron* **1996**, *52*, 5263. Space limitations preclude a complete listing of references. For a more exhaustive coverage of the literature, see also the recent references 12, 13, and 16.

(15) It is noteworthy that interpretation of inductive effects of β and γ substituents on face selectivity is inherently ambiguous. The majority of face selectivity measurements will be qualitatively consistent with either explanation. Arguments for or against electrostatic effects must entail assumptions regarding the orientation of the bond dipoles in a transition state for which mechanistic evidence is scant and qualitative (*vide infra*).

(16) These include (a) additions to alkenes [Lau, J.; Gonikberg, E. M.; Hung, J.; le Noble, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11421. Bellucci, G.; Chiappe, C.; Moro, G. L.; Ingrosso, G. *J. Org. Chem.* **1995**, *60*, 6214. Jones, G. R.; Vogel, P.; *J. Chem. Soc., Chem. Commun.* **1993**, 769], (b) photoadditions [Lau, J.; Gonikberg, E. M.; Hung, J.; le Noble, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11421. Coxon, J. M.; McDonald, D. Q. *Tetrahedron Lett.* **1992**, *33*, 651], (c) radical capture [Bodepudi, V. R.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001], (d) nucleophilic addition to carbocations [Song, I. H.; le Noble, W. J. *J. Org. Chem.* **1994**, *59*, 58], (e) sulfur oxidation [Mukherjee, A. K.; le Noble, W. J. *J. Org. Chem.* **1993**, *58*, 7955], and (f) sigmatropic rearrangements [Lau, J.; Gonikberg, E. M.; Hung, J.; le Noble, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11421].

(17) Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411.

(18) Rickborn, B.; Wuesthoff, M. T. *J. Am. Chem. Soc.* **1970**, *92*, 6894.

(19) Wigfield, D. C.; Phelps, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 543.

(20) Senda, Y.; Nakano, S.; Kunii, H.; Itoh, H. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1009.

(21) As in the earlier studies of Eliel and Senda,[17] these relative rate measurements were made on reactions involving consumption of all 4 equiv of hydride by 1 equiv of a pair of ketones.

(22) Mislow, K.; Glass, M. A. W.; O'Brien, R. E.; Rutkin, P.; Steinberg, D. H.; Weiss, J.; Djerassi, C. *J. Am. Chem. Soc.* **1962**, *84*, 1455. The structure of **1** is shown in Figure 2.

(23) (a) Fraser, R. R.; Champagne, P. J. *Can. J. Chem.* **1976**, *54*, 3809. (b) Fraser, R. R.; Stanciulescu, M. *J. Am. Chem. Soc.* **1987**, *109*, 1580. (c) Fraser, R. R.; Kong, F.; Stanciulescu, M.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 4431.

(24) The greater rigidity of **1** and three of its α methyl derivatives was established on the basis of changes in energy with distortion from the most stable conformation as calculated by molecular mechanics using the MMX program, whose validity was confirmed by agreement between their calculated energy minima and those observed in the solid state.[25]

(25) (a) Fraser, R. R.; Bensimon, C.; Kong, F.; Wu, X. *Can. J. Chem.* **1993**, *71*, 685. (b) Fraser, R. R.; Bensimon, C.; Faibish, N. C.; Kong, F. *Can. J. Chem.* **1994**, *72*, 1481.

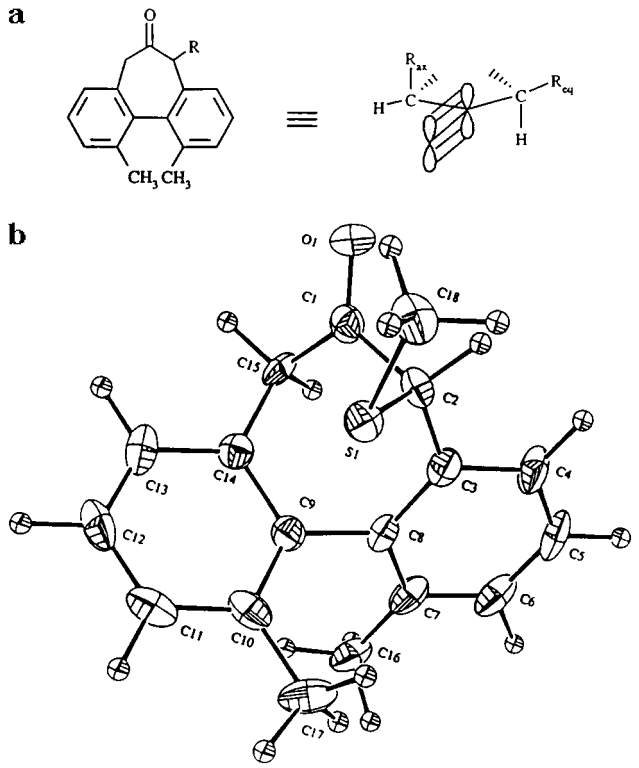

Figure 2. (a) Structural and three-dimensional representation of ketone **1** ($R_{ax} = R_{eq} = H$), its axial derivatives **2, 4, 6,** and **8** ($R_{ax} = CH_3$, Cl, OCH_3, SCH_3), and its equatorial derivatives **3, 5, 7, 9,** and **11** ($R_{eq} = CH_3$, Cl, OCH_3, SCH_3, and F, respectively). (b) An ORTEP plot of the axial methylthio derivative **8** illustrating the stereochemical properties of this ring system (numbering is for X-ray purposes only).

of **1** in our study of substituent effects on the rates of their ^{18}O exchange.[23] The two methylthio derivatives (**8**, **9**) were prepared from the reaction of the enolate of **1** with methyl methanethiolsulfonate. Equatorial fluoro ketone **11** was produced from reaction of the enolate with *N*-fluorodibenzenesulfonamide. No trace of the desired axial diastereomer **10** could be detected in the reaction mixture or after attempts to epimerize **11** in polar or nonpolarsolvents.[26] Proof of the axial orientation of the methylthio group in **8** and the equatorial disposition of the fluoro substituent in **11** was established by X-ray crystallographic analysis.

Determination of Rate Constant Ratios and Face Reactivities

A. Reductions by Lithium Aluminum Hydride in Tetrahydrofuran. In principle, this reaction could involve four different reducing agents, the aluminohydride ion and the mono-, di-, and trialkoxyaluminohydride ions.[28] Early studies by H. C. Brown and coworkers[29] have shown that for ketones in tetrahydrofuran equilibrations [1] and [2] between these ions are faster than reduction by aluminohydride which is thought to be the most reactive and thus the only reducing agent normally involved.

$$2AlH_2(OR)_2^- = AlH_3(OR)^- + AlH(OR)_3^- \quad (1)$$

$$2AlH_3(OR)^- = AlH_4^- + AlH_2(OR)_2^- \quad (2)$$

A similar conclusion was reached by Ashby and Boone[30] who studied the reduction of mesityl phenyl ketone and by Smith and Weigers[31] who used the stop−flow technique to observe second-order behavior in the reduction of camphor. However, Smith did find that more complex kinetics were exhibited during the reduction of mesityl phenyl ketone in diethyl ether[32] suggesting equal involvement of aluminohydride and monoalkoxyaluminohydride ions in this solvent. At room temperature this reduction took less than 60 s.

For our studies the rapidity of the reaction made it necessary to measure the relative rates of reduction of ketones **1**−**9** and **11** in pairs. The reaction conditions, arrived at by preliminary examination of effects of concentration, moisture, and reaction times, were chosen to minimize the hydride consumption and thereby the involvement of mono- or dialkoxyaluminohydrides. Using a temperature of 0 °C and a reaction time of 20 s, we were able to measure rate ratios from quenched reactions in which the consumption of hydride seldom exceeded 60% of the total available hydride.[33]

To provide evidence supporting the involvement of AlH_4^- as the sole or major hydride donor, we carried out nine measurements of the ratio of rate constants from reactions involving three differing proportions of **1** and **2**. The results appear in Table 1. For equimolar mixtures and for 1:3 mixtures of **1** and **2**, the value for k_{Me}/k_H was consistently at 0.41 + 0.02. For a 3:1 mixture the ratio was lower, averaging 0.33 for two runs. We suspect that the decrease in the latter runs is due to incomplete equilibrations via [1] and [2], resulting in the involvement of alkoxyaluminohydride ions in reductions of both **1** and **2** (possibly equilibration is sterically accelerated in the alkoxyaluminohydrides of **2**). The decrease in the rate constant ratio and the smaller extent of reduction for the mixtures rich in **1** are consistent with this interpretation. For further evidence, we "formally" produced the dialkoxyaluminohydride of **1** by pretreating a solution of LAH with 2 equiv of **1** prior to the addition of 1 equiv each of **1** and **2**. Standard analysis of the product after quenching showed k_{Me}/k_H of 0.33. This decrease is also consistent with the involvement of some alkoxyaluminohydride whose increased size selectively retards its reactivity toward **2**. The rate constant ratio showed a further decrease to 0.20 when lithium tributoxyaluminohydride was used as reducing agent. The reproducibility in the values (0.414 ± 0.02), for the rate constant ratios in runs 1−5 and 7, supports our contention that in these runs the reductions were performed by AlH_4^- ion.

Calculation of Face Reactivities. Ketone **1**, by virtue of its C_2 axis, yields on reduction the single alcohol **12** whose 300 MHz spectrum apppears in Figure 3. In this spectrum the four benzylic protons apppear as four-line patterns in each of which the vicinal splittings varies with its dihedral angle with respect to the methine proton at C6. The spacings of 10.1, 6.4, 4.8, and 1.8 Hz for the

(26) We are confident that even 0.5% of **10** would have been observable in our search using 500 MHz ^1H NMR. Our concomitant study of the magnitudes of axial preference in α-substituted cyclohexanones[27] revealed the fluoro substituent to have the strongest preference for the equatorial position in that system as well.

(27) Fraser, R. R.; Faibish, N. C. *Can. J. Chem.* **1995**, *73*, 88.

(28) Boone, J. R.; Ashby, E. C. *Top. Stereochem.* **1979**, *11*, 53.

(29) (a) Brown, H. C.; McFarlin, R. F. *J. Am. Chem. Soc.* **1958**, *80*, 5372. (b) Brown, H. C.; Shoaf, C. J. *J. Am. Chem. Soc.* **1964**, *86*, 1079.

(30) Ashby, E. C.; Boone, J. R. *J. Am. Chem. Soc.* **1976**, *98*, 5524.

(31) Wiegers, K. E.; Smith, S. G. *J. Org. Chem.* **1978**, *43*, 1126.

(32) Wiegers, K. E.; Smith, S. G. *J. Am. Chem, Soc.* **1977**, *99*, 1480. See also: Brown, H. C.; Deck, H. R. *J. Am. Chem. Soc.* **1965**, *87*, 5620.

(33) As long as hydride interchanges [1] and [2] are fast relative to reduction, up to 75% consumption of available hydride should involve AlH_4^- as the reducing agent.

Table 1. Competitive Reduction of Ketones 1 and 2 with LAH in THF at 0 °C (20 s Quench, 0.05 mmol of Total Ketones)

entry	ketone **1**: ketone **2**	$LiAlH_4$ mmol	%**1** reduced	%**2** reduced	% total hydride consumed	k_2/k_1
1	1:2.7	0.006	45	22	58	0.410
2	1:2.6	0.003	51	30	74	0.488
3	1:1.7	0.00275	63	32	87	0.388
4	1:2.7	0.006	54	26	69	0.391
5	1:1.1	0.006	34	15	50	0.398
6	2.8:1	0.006	23	9.0	29	0.333
7	1:1	0.006	30	14	38	0.412
8	3.1:1	0.006	22	7.6	40	0.322

[a] 0.025 mmol of total ketones in 10 mL. [b] 0.022 mmol of total ketones.

absorptions at δ 2.05, 2.59, 2.43, and 2.34, respectively, are assigned to the protons having dihedral angles of 160° (H_a), 40° (H_b), 40° (H_d), and 80° (H_e) as depicted in Figure 4. Also seen are the geminal splittings between H_a and H_b (12.4) and H_d and H_e (14.0 Hz). For ketone **2**, in which the methyl substituent is quasi-axial, addition of hydride to the carbonyl may occur either *app* to the methyl yielding the *cis* alcohol **13**[34] or *synperiplanar (sp)* yielding the *trans* alcohol **14**. Reaction of a 1:1 mixture of **1** and **2** with LAH in tetrahydrofuran at 0 °C for 20 s, followed by quenching with acid, gave a mixture of the three alcohols and unreacted ketones which was examined by proton NMR at 500 MHz. This spectrum is shown in Figure 5. Measurement of the integral ratios for the absorptions of **1** in the methylene region versus **12** and **13** in the methine region and **2** versus **13** and **14** in the methyl region provided all final relative concentrations. Treatment of the competitive reduction of the mixture as two pseudo-first-order reactions provided $k_1 = \log [\mathbf{1}]_o/[\mathbf{1}]_f$ and $k_2 = \log [\mathbf{2}]_o/[\mathbf{2}]_f$ where $[\mathbf{1}]_o = [\mathbf{1}]_f + [\mathbf{12}]$ and $[\mathbf{2}]_o = [\mathbf{2}]_f + [\mathbf{13}] + [\mathbf{14}]$. Representing attack at both faces, $k_2 = k^{app} + k^{sp}$ and since the observed diastereoselectivity (k^{app}/k^{sp}) was 11.9, then $k_2 = 1.08k^{app}$ or $k^{app} = k_2/1.08$. From the value for the rate constant ratio in Table 2, $k_2 = 0.414k_1$ and $k^{app} = 0.383k_1$ or $k^{app}/k_1 = 0.383$. The face reactivity, expressed relative to a single face of **1**, will then be twice as large or $k^{app}/k_H = 0.77$.

In a similar way pairwise measurements of the reduction products of **3**−**11** versus **1** provided their rate constant ratios listed in Table 2. For each entry the number of measurements made and the diastereoselectivity are also given. The results of conversion of these data into the face reactivities, k^{app}/k_H for the axial derivatives and k^{ac}/k_H for the equatorial derivatives, appear in the last column of the table.

B. Reduction by Sodium Borohydride in Isopropyl Alcohol. In contrast to the reductions involving LAH, the order of reactivities of the four reducing species is reversed with borohydride being the least reactive ion followed by mono-, di-, and trialkoxyborohydrides.[35] In most reductions, equilibration between the four ions has not been detectable, although exceptions have been noted.[18,35] In an exploratory examination of reaction conditions 1 equiv of each of ketone was stirred with 1 equiv of sodium borohydride in 2-propanol at 23 °C and aliquots were taken and quenched at varying intervals. From the observed conversions, a reaction time was then selected to limit the consumption of borohydride to less than 10% of available hydride.[36] In reductions of the axial methylthio and methoxy derivatives, small amounts of up to 3% of epimerization were observed and corrected for (see Experimental Section for details). Analysis of the quenched products by proton NMR as described in A above provided the rate constant ratios and the face reactivities derived therefrom which appear in Table 2.

C. Boron Trifluoride-Catalyzed Reductions by Triethylsilane in Acetonitrile. Pairwise reduction of the ketone mixture in acetonitrile at 0 °C was carried out using 1 equiv of triethysilane and 3 equiv of boron trifluoride. Because fluoroborate esters[37] have been identified as products of the reaction [3],

$$\mathrm{RCOR'} + (\mathrm{C_2H_5})_3\mathrm{SiH} \overset{\mathrm{BF_3}}{\Rightarrow} \mathrm{RCH(OBF_2)R'} + (\mathrm{C_2H_5})_3\mathrm{SiF} \quad (3)$$

minimal reaction times and 3 equiv of catalyst were used to limit reduction to 10% and catalyst modification to 3%.[39] After quenching and hydrolysis, standard analysis of the reaction mixture gave the rate constant ratios and face reactivities listed in Table 2.

Results and Discussion

General Features. To see if our face reactivities k^{app} and k^{ac} showed a correlation with the inductive effects of the α substituents, a plot of log k against the inductive substituent parameter σ_I[40] was made for each reduction. A linear plot is said to follow the Taft equation,[41] $\log k = \rho\sigma_I$ where the slope ρ represents the susceptibility constant. Plots of face reactivities for the three reducing agents appear in Figure 6a−c. In all cases correlations with σ_I are evident.[42] For reductions involving LAH the slopes for the two Taft plots of axial and equatorial derivatives are similar, 1.4 for k^{app} and 1.1 for k^{ac} with r, the correlation coefficient, being 0.89 and 0.84, respectively. Slightly better correlations ($r = 0.92$ in each series) are seen for plots of the face reactivities toward BH_4 ion and the slopes are much larger, being about 4.2 and 3.3 for plots involving k^{app} and k^{ac}, respectively. Although the Taft correlations are poor for the reactions

(34) The assignment of stereochemistry to each pair of diastereomeric alcohols is based on the magnitude of the vicinal coupling constants between the protons at C5 and C6. The proton spectrum of the major alcohol **13** typically lacks a large vicinal splitting (for the dihedral angle of 160°) as a consequence of hydride addition *app* to the axial substituent. The spectrum for the major alcohol resulting from addition *ac* to the equatorial substituent is identifiable by its lack of the very small splitting (<2 Hz) associated with an 80° dihedral angle. Figures 4b and 4c depict these stereochemical arrangements.

(35) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449.

(36) The consumption of hydride has been minimized to restrict epimerization and the rearrangement of the substituted ketone both of which increase as the reaction progresses.

(37) Although the BF_3-catalyzed reaction was first carried out by Doyle[38] in BF_3·ether, we found that the reduction of **1** was remarkably free from any side products when run in acetonitrile.

(38) Doyle, M. P.; West, C. T.; Donnelly, S. J.; McOsker, C. C. *J. Organomet. Chem.* **1976**, *117*, 129.

(39) In one instance reduction of the axial methoxyl was accompanied by a product of rearrangement and reduction, for which a correction in the calculated rate ratio was made.

(40) For a comprehensive list of review articles, see: Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row: New York, 1987; p 143, ref 28. See also: Taft, R. W., Jr. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; John Wiley & Sons: New York, 1956; pp 607−610.

(41) (a) Taft, R. W., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 3120. (b) Taft, R. W., Jr. *J. Am. Chem. Soc.* **1953**, *75*, 4231.

(42) We have chosen to use the values of Exner, $\sigma_I(\mathrm{Me}) = -0.06$, $\sigma_I(\mathrm{H}) = 0$, $\sigma_I(\mathrm{SMe}) = 0.22$, $\sigma_I(\mathrm{OMe}) = 0.31$, $\sigma_I(\mathrm{Cl}) = 0.51$, and $\sigma_I(\mathrm{F}) = 0.56$ (as cited by Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119−251, p 171), as they proved to provide excellent correlations in reactions involving addition of pinacolone lithium enolate to α-substituted ketones; Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* **1993**, *115*, 1302.

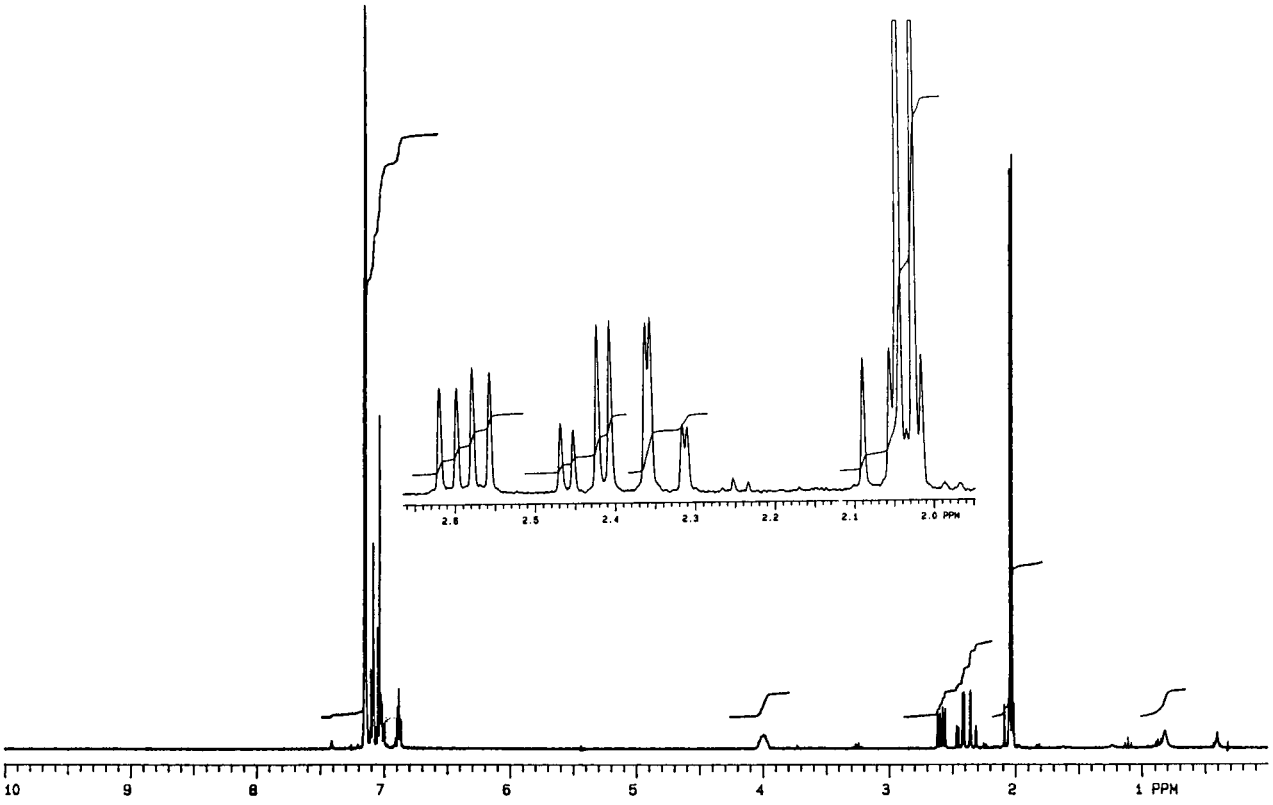

Figure 3. ^{1}H NMR spectrum (500 MHz) of alcohol **12**.

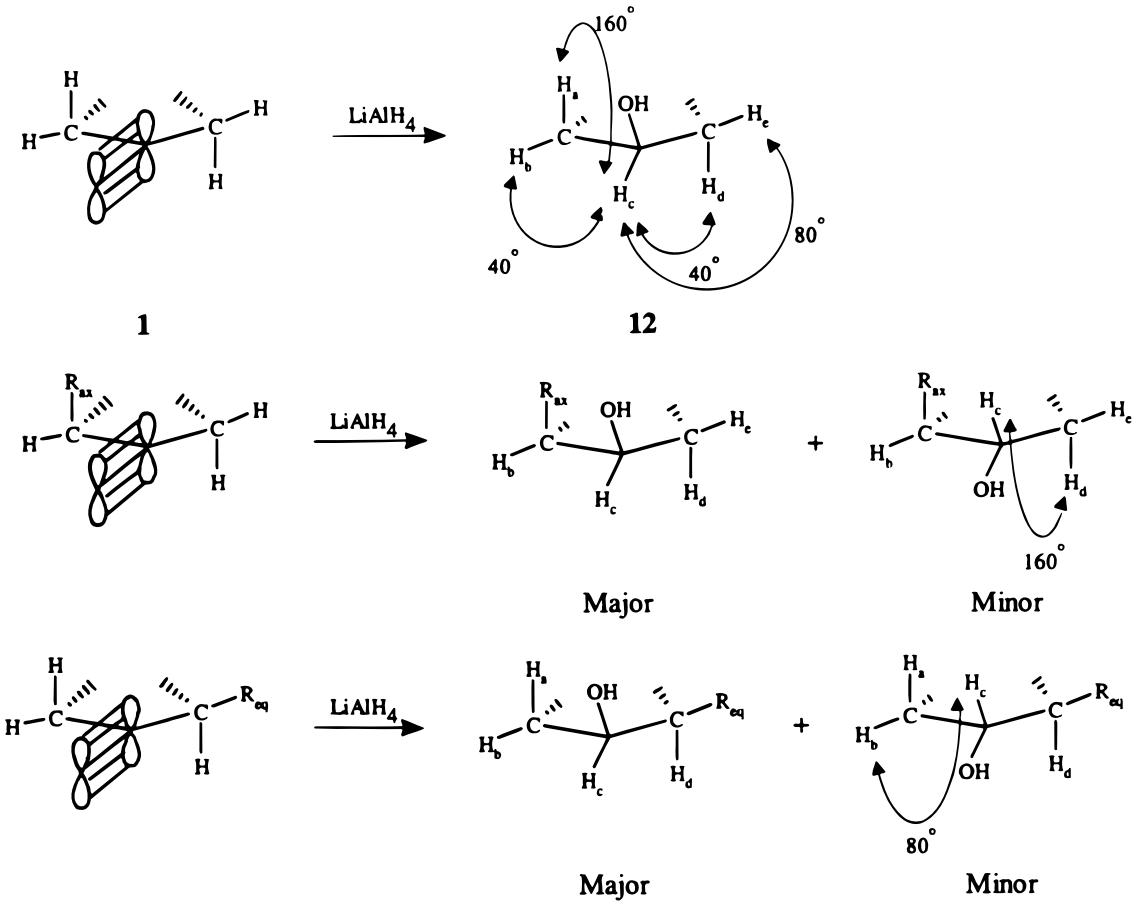

Figure 4. Dihedral angular relationships between vicinal protons in alcohols formed by hydride addition (a) to parent ketone **1**, (b) *app* to an axial derivative, (c) *ac* to an equatorial derivative.

involving triethylsilane, it appears that the slopes for these two plots are negative, and larger for the axial than equatorial series.

The sign and magnitude of the slope ρ in a Taft plot provides information on the transition state for the reaction involved. The observation of a positive slope

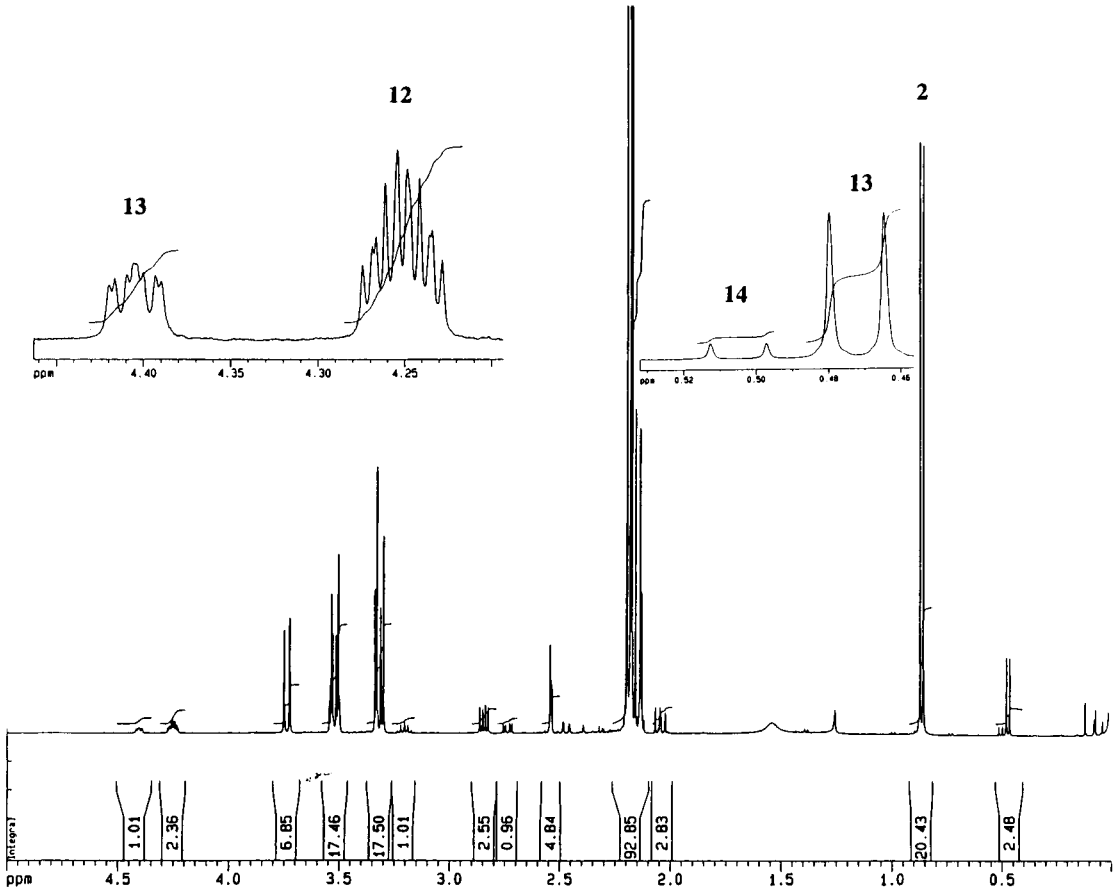

Figure 5. ^{1}H NMR spectrum (300 MHz) of the crude obtained from LAH reduction of a 1:1 mixture of 1 and 2. Expansion of the regions δ 4.2−4.5 and δ 0.4−0.5 appear in inserts above the main spectrum.

Table 2. Face Reactivity[a] of the α Derivatives of 1

substituent R	k_R/k_{unsub}			π-facial selectivity[c]			k_R^{app}/k_H		
	$LiAlH_4$	$NaBH_4$	Et_3SiH	$LiAlH_4$	$NaBH_4$	Et_3SiH	$LiAlH_4$	$NaBH_4$	Et_3SiH
H				1.0	1.0	1.0	1.0	1.0	1.0
CH_{3ax}	0.405 (8)[b]	0.114 (2)	0.155 (1)	11.9	6.5	11.5	0.77	0.20	0.28
SCH_{3ax}	0.436 (4)	0.390 (2)	0.00861 (1)	≥19			0.87	0.78	0.017
OCH_{3ax}	1.36 (1)	8.18T(1)	0.185 (2)	≥19	≥19	≥19	2.7	16.4	0.37
Cl_{ax}	2.81 (1)	40.0 (2)	0.0024 (1)	≥19	≥19		5.6	80	0.0048
							k_R^{ac}/k_H		
CH_{3eq}	1.12 (3)	0.454 (2)	0.156 (1)	4.5	~2	~2	1.8	0.91	0.31
SCH_{3eq}	2.27 (2)	4.34 (1)	0.0915 (2)	≥19	≥19	≥19	8.1	84	1.8
OCH_{3eq}	4.07 (2)	42.1 (2)	0.921 (2)	≥19	≥19	≥19	8.1	84	1.8
Cl_{eq}	3.31 (2)	20.0 (3)	0.0659 (1)	8.2	5.3	7.0	5.9	34	0.12
F_{eq}	3.68 (4)	60.0 (2)	0.134 (1)	7.6	5.9	7.9	6.5	103	0.27

[a] See Experimental Section and Appendix 2 for precision. [b] The number in parentheses gives the number of measurements. [c] Blank regions were not determinable due to poor signal to noise.

indicates an increase in the amount of negative charge in conversion of ground state to transition state. A value of 1 for the slope indicates a similar amount of charge development as in the standard reaction[40] but in only a qualitative manner as solvent effects on ρ are known to be substantial.[43] Table 3 summarizes the results of least-squares analyses of the plots in Figure 6. Thus the slopes of about 1.4 for the reductions by LAH are consistent with a transition state having only a small amount of negative charge on the carbonyl oxygen. The 2-fold larger values for ρ in the plots of the borohydride reductions indicate much greater charge development in a later transition state.[44] For the BF_3-catalyzed reduction the change to a negative slope in the plot of k^{app} vs σ_I is in keeping with the development of appreciable positive charge at the carbonyl group in the transition state. The three transition states, proposed earlier by Ashby,[30], Wigfield,[34] and Doyle,[38] are presented in Figure 7. It is noteworthy that each of them has the coordination of the carbonyl group to a Lewis acid, Li^+, 2-propanol, and BF_3 in a, b, and c, repectively.[45] It is thus not surprising that the transition state c bearing the bulky triethylsilyl group has sufficient spatial requirements to enable a sizeable α substituent to sterically perturb the normal Taft relationship[46] and give rise to the weakest of our correlations involving k^{app} in Figure 6c. From all these plots it is clear that the

(43) Solvent effects on ρ can be expected to resemble those reported for Hammett plots, ref 40, p 146.

(44) Variations in ρ are described in Taft's review,[41c] p 606.

(45) The Lewis acid coordinated to the ketone in a and c is expected to lie in the nodal plane of the π bond of the carbonyl as established by X-ray for a methylaluminum diaryloxide complex of benzophenone; Power, M. B.; Bott, S. G.; Atwood, J. L.; Barron, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 3446.

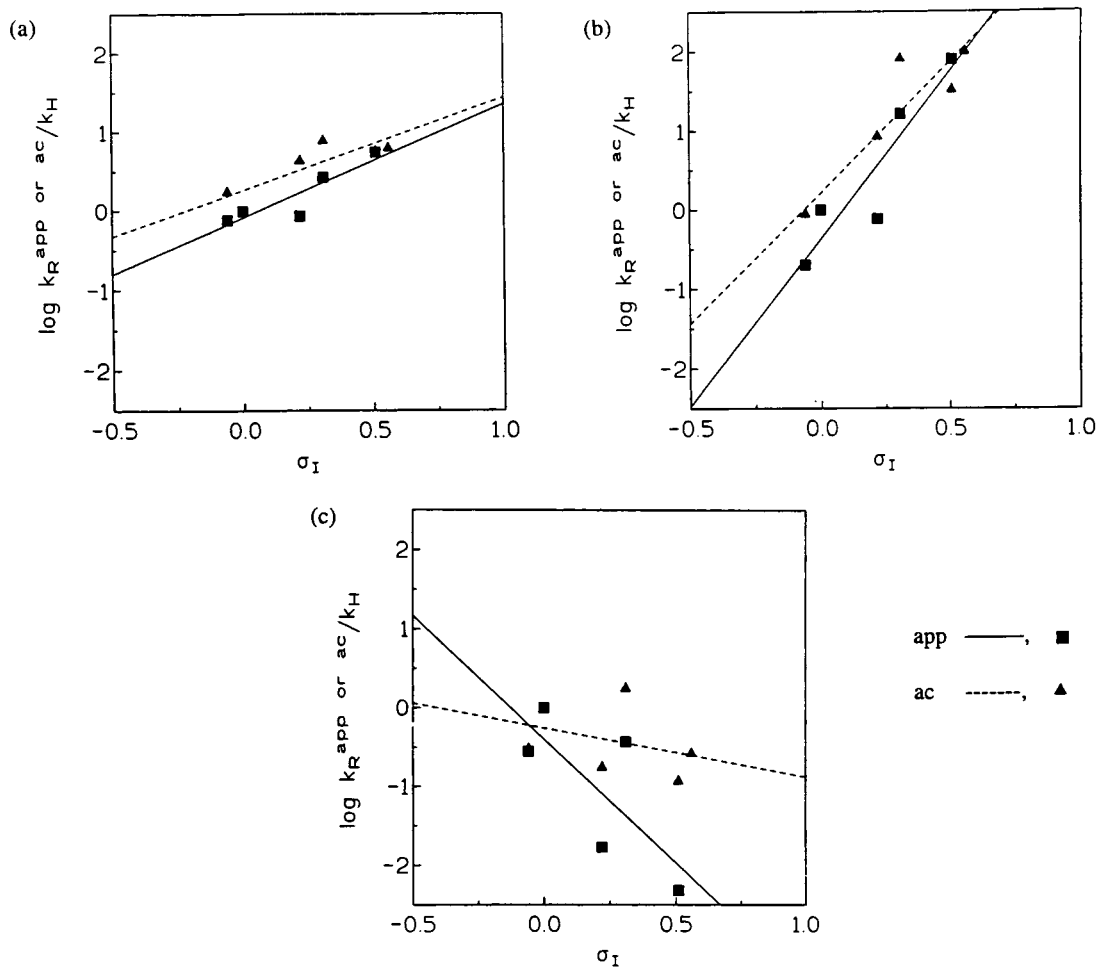

Figure 6. Taft plots of face reactivity versus the α substituent parameter σ_I for reductions by (a) LAH in tetrahydrofuran, (b) SBH in 2-propanol, (c) triethylsilane in acetonitrile containing BF_3 etherate.

Table 3. Correlation Coefficients and Susceptibility Constants for the Taft Plots

	$LiAlH_4$		$NaBH_4$		Et_3SiH	
	app	*ac*	*app*	*ac*	*app*	*ac*
r (correlation coefficient)	0.896	0.840	0.922	0.919	−0.743	−0.353
ρ (slope)	1.44	1.18	4.22	3.31	−3.14	−0.624

inductive effects of the α substituents are mainly responsible for the variations in k^{app}, regardless of the type of charge development in the transition state. Consequently, the presence of any *antiperiplanar* orbital interaction ought to be most evident in the reduction least influenced by inductive effects, that involving LAH.

Individual Axial Substituent Effects in LAH Reductions. (i) Methyl. On the basis of the 9:1 diastereoselectivity in the LAH reduction of cyclohexanone, there is a 1.35 kcal preferential stability for the axial transition which is attributed by Cieplak to the stabilizing interaction provided by two app C−H versus C−C bonds. For reduction of **2** versus **1** we should expect, in the absence of inductive[47] or steric factors, to see 0.7 kcal/mol of destabilization since in **2** one *app* C−H bond has been replaced by a methyl group. Experimentally, we see a 23% decrease in face reactivity for this structural change, which amounts to 0.15 kcal/mol of destabilization, a much smaller effect than expected from either Cieplak's or Anh's theory.[48] **(ii) Methylthio Substituent.** Cieplak has predicted that the C−S bond of this substituent when *app* should have a stronger stabilizing effect than a C−H bond when interacting with the incipient bond of the transition state. Experimentally, the face reactivity for an *app* methylthio substituent indicates it to be slightly destabilizing. **(iii) Chloro and (iv) Methoxy.** Replacement of hydrogen by either of these substituents has been predicted by Cieplak to retard attack at the *antiperiplanar* face of a carbonyl. However, both substituents show an accelerating effect. Thus any retarding influence, if present, must be significantly smaller than the observed dominant inductive stabilization of 0.6 for the chloro and 1.0 kcal/mol for the methoxy substituent. In summary, none of the effects of the axial substituents obey the predictions of Cieplak for *app* attack by LAH.

Individual Axial Substituent Effects in Reductions by Sodium Borohydride. Of the four axial substituents, only the methyl affects the face reactivity in the direction predicted by Cieplak. Its introduction increases the free energy of activation by 1.0 kcal/mol. The methylthio group causes a slight decrease in face reactivity while both the methoxy and chloro substituents cause large increases in face reactivity.

(46) Field effect contributions and limitations to the success of Taft correlations are discussed in Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley-Interscience: New York, 1975; pp 32−37 and 92−95.

(47) The σ_I value of −0.06 for a methyl substituent is considered negligible.

(48) Anh's calculations predicted the *app* methyl and chloro groups to provide 1.9 and 23.5 kcal/mol of stabilization, respectively. Because Cieplak has proposed their effects to be destabilizing, all reactivities found to be in accord with his theory will be in opposition to Anh's and vice versa.

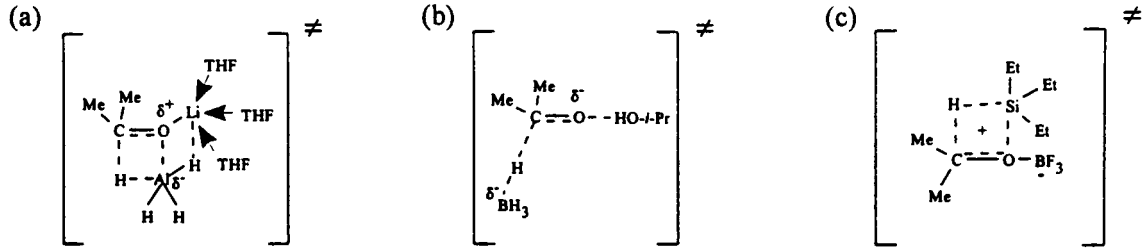

Figure 7. Transition states proposed for reductions by (a) LAH, (b) SBH, and (c) triethylsilane.

Individual Axial Substituent Effects in Reductions by Triethylsilane. In this reaction all four substituents cause a decrease in face reactivity with the effect of the methylthio group being the only exception to Cieplak's prediction. The methoxyl group is the main deviant from linearity in the Taft plot.

Stereochemical Dependence of Substituent Effects. In order for the Cieplak or Anh Effect to be operative there must be an *antiperiplanar* arrangement of the two interacting orbitals. Consequently the orbital overlap should be optimal for interaction of the incipient bond with that to an axial (*app*) substituent but minimal with that to an equatorial (*ac*) substituent. If the inductive and steric effects are assumed to be independent of stereochemistry,[49] a comparison of the effect of the substituent when axial with that when it is equatorial should reveal the presence of any orbital interaction.

(a) Reductions by LAH. Examination of Figure 6a shows k^{app} for the axial methyl to be smaller than k^{ac} for the equatorial. Thus the methyl group when axial decreases the face reactivity relative to that for the equatorial derivative as proposed by Cieplak. The methoxy group shows the same stereochemical influence, i.e., k^{app} is less than k^{ac} as predicted Cieplak. But for the methylthio group a smaller k^{app} than k^{ac} is in opposition to his theory. The stereodependence of the chloro substituent is negligibly small, less than 0.1 kcal/mol.

(b) Reductions by Sodium Borohydride. The stereodependence of face reactivity for the four substituents show similar extents of adherence to Cieplak's theory as with LAH reductions. The influence of methyl and methoxy groups is in agreement, while that of the methylthio and chloro groups is not.

(c) Triethylsilane Reductions. In these BF_3-catalyzed reductions the face reactivities were the same for both axial and equatorial methyl derivatives and slower for axial than equatorial methylthio, each stereodependence being at odds with the expectations based on Cieplak's theory. For methoxy and chloro substituents, the changes in face reactivity with stereochemistry were in accord with his theory.

In summary, for the 12 comparisons of the influence of substituent orientation on face reactivity, six are consistent and six inconsistent with the requirements for orbital alignment implicit in Cieplak's theory. Therefore, none of the data on face reactivities are able to provide supporting evidence for his or Anh's theory.

A Closer Look at the Taft Correlations of Face Reactivity

The original inductive substituent parameters of Taft[41] were defined by a series of measurements of the rates of acid- and base-catalyzed hydrolyses of a series of α-substituted acetates, XCH_2COOR, according to the following equation:

$$\sigma = 1/2.48\,[(\log k_X/k_H)_B - (\log k_X/k_H)_{HA}]$$

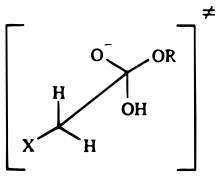

Figure 8. Taft transition state for base-catalyzed hydrolysis.

By design, this constant should reflect the influence of X on the free energies of activation, $\Delta G^{\ddagger}$ (relative to hydrogen), in forming the two transition states for hydrolysis. Since they differ only in the presence of two protons, steric effects therein should cancel, resonance effects should be prevented by the intervening methylene group, and X should exert its influence by its inductive effect only.[50] The standard pair of reactions chosen by Taft to provide the inductive substituent constants involves acyclic esters. But for the reaction involving the addition of hydride ion to cyclic ketones **1**−**11** conformational effects may play an important role. As seen in Figure 8 the transition state for hydrolysis has three C−O bonds at the reaction site adjacent to a freely rotating XCH_2 group. The transition state for addition has three very different bonds at the ketone carbonyl and an XCHR group whose configuration and conformation are fixed. The rigid character of this latter transition state will result in a significantly different field component of the inductive effect of X.[52] As depicted in Figure 9a the linear chloro substituent, when equatorial, has the negative end of the C−Cl dipole closer to the positive charge in the transition state for reduction by triethylsilane than when axial, leading to its greater stabilization and enhanced reactivity in *ac* vs *app* addition. In the transition states for borohydride addition shown in Figure 9b, the negative end of the C−Cl dipole will be closer to the developing negative charge when equatorial, leading to greater destabilization and reduced reactivity in *ac* versus *app* addition. In the LAH reductions the

(49) This assumption, also made by Cieplak, Tait, and Johnson[7] in interpreting their data in terms of an orbital interaction is not justified, as discussed below.

(50) It is now recognized that there are two modes of transmission of an inductive effect, (ref 46, pp 32−36) through the intervening bonds or through space (alternatively called a field or electrostatic effect). Numerous attempts have been made to determine to what extent each contributes. Currently, both modes are considered to be comparable.[51]

(51) (a) Reynolds, W. F. *J. Chem. Soc. Perkin Trans. 2* **1980**, 985. (b) Bowden,K.; Grubbs, E. J. *Prog. Phys. Org. Chem.* **1993**, *19*, 183.

(52) The magnitude of an electrostatic effect can be calculated rigorously from the interaction of point charges according to Coulomb's law, or from the interaction of bond dipoles using an approximate relationship.[2,46] The accuracy of either method is limited by the estimate of charge distribution in the transition state, as well as the uncertainty of the value selected for the dielectric constant of the medium.

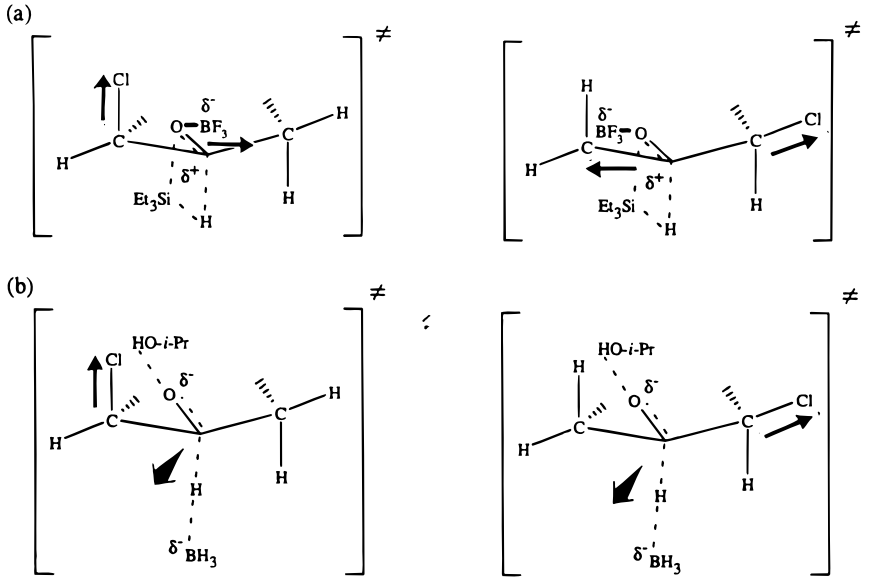

Figure 9. Comparison of the proposed transition states for (a) BF_3-catalyzed reduction of axial and equatorial chloro derivatives **4** and **5** and (b) SBH reduction of **4** and **5**.

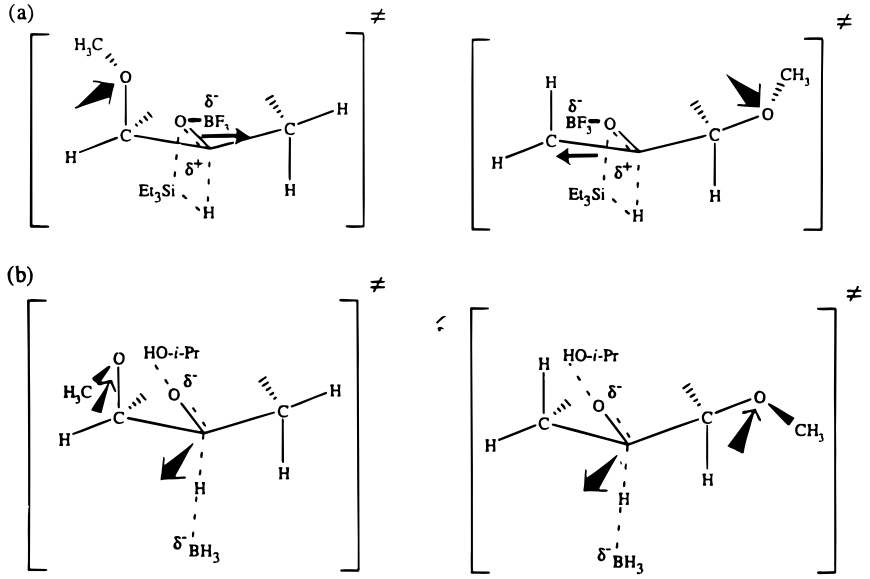

Figure 10. Comparison of the proposed transition states for (a) BF_3-catalyzed reduction of axial and equatorial methoxyl derivatives **6** and **7** and (b) SBH reduction ofderivatives **6** and **7**.

electrostatic effect of chloro will similarly favor the axial transition state, but to a lesser extent, as expected for a reaction having a smaller ρ in the Taft plot.

For the methoxy and methylthio derivatives, the field component of their inductive effects is influenced by an additional factor, the ability of the substituent to adopt either of two stable conformations.[53] In Figure 10a the transition state for reduction of the equatorial methoxy derivative by triethylsilane will be stabilized relative to the axial by the favorable interaction of the methoxyl oxygen atom with the positively charged transition state and by adopting the conformation in which the attached methyl avoids the positive charge by being trans to the carbonyl group.[53] In the transition state in Figure 10b for reduction by borohydride, the repulsive Coulombic interaction between the equatorial methoxyl oxygen and the negative charge in the transition state is more than offset by its strong attractive interaction with the methoxyl carbon now in a conformation gauche to the carbonyl. For the axial derivative such an interaction will be strongly attenuated by distance. These considerations for the methoxyl group should apply equally well to the methylthio group since the C−S bond has a larger group dipole moment than the C−O bond.[54] In the transition states for the LAH reductions the same effects should selectively enhance the reactivity of the equatorial diastereoisomer, albeit less strongly due to the decreased charge development.

This interpretation for the consistently faster reductions of equatorial over axial *O*-methyl and *S*-methyl derivatives for all three reactions[55] provides additional support for the importance of electrostatic interactions

(53) In the parent ketones **6** and **8**, the two conformations with the methyl group gauche to the vicinal hydrogen have the same stability, with the third conformation being more than 3 kcal/mol higher in energy as calculated using the MMX program PCMODEL.

(54) Smyth, C. P. *J. Chem. Phys.* **1937**, *5*, 209. The strong dipole associate with the C−S bond may seem surprising in view of the electronegativity values for carbon and sulfur. A better reflection of the polarity of the methylthio group is provided by its σ_I value, which is similar to that of a methoxyl on any accepted scale.[46,51]

in accounting for stereodependent substituent effects.[10] That our stereodependence of face reactivity on the presence of α substituents is larger ($\Delta\Delta G^{\ddagger} = 0.7-1.5$ kcal/mol) than that observed[10] for face selectivity on γ substituents ($\Delta\Delta G^{\ddagger} = 0.2-0.8$ kcal/mol) reflects their strong distance dependence (pole−dipole and dipole−dipole interactions are inversely proportional to r^2 and r^3, respectively).[2,46]

Summary

The face reactivities for three reactions involving addition of hydride ion to a series of α-substituted ketones have shown Taft correlations with the inductive effects of the substituents. Neither the effect of substituents on the face reactivity for *app* addition nor comparison of the axial−equatorial differences in *app* versus *ac* addition consistently support either the Cieplak effect or the antiperiplanar effect of Anh. The effects are explicable on the basis of a combination of through-bond and through-space (electrostatic) interactions in the transition state.

Experimental Section

General Experimental. Melting points are uncorrected. Thin-layer chromatography was performed using a commercial preparation (DC-Alufolien Kieselgel 60 F_{254} EM Separations Technology) and viewed using ultraviolet light. Chromatography was performed under a steady stream of nitrogen using 230−400 mesh flash grade silica gel (equivalent to Merck 9385). Radial chromatography was performed with a Chromatatron using silica gel 60-F254 rotors (1, 2, or 4 mm thickness). Mass spectra were obtained using a V6 7070-E spectrometer (EI).

All ^{1}H NMR and ^{13}C NMR spectra were recorded on spectrometers operating at 500, 300, and 200 MHz for protons and 125.7, 75.4, and 50.3 MHz for carbons, respectively. Spectra were recorded in $CDCl_3$ (purchased from Cambridge Isotope Laboratories), and chemical shifts are given in ppm relative to Me_4Si (0 ppm, ^{1}H) or $CDCl_3$ (77 ppm, ^{13}C) unless otherwise indicated.

All air and/or moisture sensitive reactions were performed under argon with oven-dried glassware (120 °C) using standard syringe−septum cap techniques. A −78 °C bath refers to a mixture of dry ice in acetone. All solvents (reagent grade) and reagents were obtained from commercial sources and used without further purification unless otherwise specified. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone ketyl under an argon atmosphere. Acetonitrile and 2-propanol were distilled from calcium hydride under an argon atmosphere prior to use. Hexanes used for chromatography was distilled prior to use. Solutions of MeLi in Et_2O (1.6 M) were purchased from Aldrich and titrated with diphenylacetic acid before use. Solutions of lithium aluminum hydride in THF were prepared freshly before use.

The plots and their least-squares analyses were obtained using the commercially available Graphpad Inplot Software v. 4.03.

Syntheses. Compound **1** was synthesized as described in the literature.[22]

The preparation of **2**−**7** was carried out as described in the literature[23b,25] except for the α-chloro and α-methoxy ketones whose final purification procedures were slightly modified. The isolation of **4** was performed by flash column chromatography using Et_2O:AcOH:hexanes (2:1:100 v/v/v) as the eluent. The partial separation of **4** and **5** gave reproducibly a maximum **4**:**5** ratio of 2.5:1 (and <10% of dichloro-disubstituted derivatives of **1**). Similarly, the separation of **6** and **7** was carried out by flash column chromatography employing Et_2O:AcOH:hexanes (4:1:100 v/v/v) as the eluent. In both instances, the elution of products was complete within 10−15 min. The purified or enriched (for ketone **4**) samples were subsequently used for our π-facial reactivity study.

5-(Methylthio)-5,7-dihydro-1,11-dimethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-one (8, Axial). To a stirred solution of LHMDS (2.1 mmol, prepared at 0 °C from methyllithium and 1,1,1,3,3,3-hexamethyldisilazane (Aldrich) and allowed to stir for 1 h) in THF (1 mL) was added dropwise a solution of ketone **1** (473 mg, 2.0 mmol) in THF (2 mL) at −78 °C, and then the temperature was raised to 0 °C. After 1 h at 0 °C, the solution was cooled to −78 °C and methyl methanethiolsulfonate[56] (purchased from Aldrich; 206 μL, 2.0 mmol) in THF (1 mL) was added and stirring was continued for 0.5 h at −15 °C. The reaction mixture was quenched with ∼1 mL of 0.75 N HCl, concentrated to remove the THF, and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product (652 mg) was purified by flash column chromatography using Et_2O:hexanes (1:50 v/v) as eluent. Recrystallization from ether−hexanes afforded **8** (243 mg) in 43% yield (unoptimized): mp 110−113 °C; $R_f = 0.31$ (Et_2O:hexanes, 1:5 v/v); ^{1}H NMR (500 MHz) 7.28−7.22 (m, 4H), 7.12−7.10 (m, 2H), 3.98 (s, 1H), 3.55 (AB q, 2H, $J = 14.6$ Hz), 2.18 (s, 3H), 2.17 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (125.7 MHz) 205.8, 137.9, 137.6, 136.8, 136.6, 136.4, 132.4, 130.5, 129.0, 128.1, 127.5, 127.2, 125.9, 60.4, 48.3, 19.9, 19.6, 18.8; HRMS calcd for $C_{18}H_{18}OS$ (M^+) m/z 282.1078, found 282.1080.

NOE difference measurements of **8** were performed on a sealed degassed sample (5 mg) in 0.5 mL of $CDCl_3$. Irradiation of the methine proton at C5 caused a 20% increase in the integral for the ortho aromatic proton at C4.

A suitable sample for X-ray analysis[57] was obtained by recrystallizing **8** from ether−hexanes. An ORTEP plot of **8** appears in Figure 2b and in the Supporting Information.

5-(Methylthio)-5,7-dihydro-1,11-dimethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-one (9, Equatorial). Method A. Compound **9** was obtained by isomerization of **8**. To a stirred solution of **8** (95 mg, 0.34 mmol) in acetonitrile (10 mL) was added sodium methoxide (24 mg, 0.57 mmol) at rt for 1 h. The solution was concentrated under vacuum and partitioned between ether (3 × 10 mL) and water (2 mL). The combined organic extracts were washed with water, dried (Na_2SO_4), and evaporated to a syrup (93 mg, **9**:**8**, 1:2.4). Purification by flash column chromatography over silica gel (150 fold, 13.95 g) using AcOH:Et_2O:hexanes (1:2:100 v/v/v) as eluent yielded after concentration a maximum **9**:**8** ratio of ∼1:1 for the early fractions ($R_f = 0.31$, Et_2O:hexanes, 1:5 v/v). An appropriate pressure of N_2 was used to complete the chromatography within a maximum of 10−15 min. **Method B.** Ketone **9** was prepared by concentrating the mother liquor solution from the synthesis of **8**. Purification by flash column chromatography as described in method A yielded after concentration a maximum **9**:**8** ratio of 6:1 for the early fractions: ^{1}H NMR (500 MHz) in the presence of **8**, 7.64−7.63 (m, 1H), 7.36−7.07 (m, 5H), 4.77 (s, 1H), 3.45 (AB q, 2H, $J = 16.8$ Hz), 2.26 (s, 6H), 1.93 (s, 3H); ^{13}C NMR (125.7 MHz) 204.8, 137.2, 137.0, 134.7, 133.1,130.0, 129.6, 128.1, 127.8, 126.4, 123.5, 61.1, 47.9, 19.9, 14.2; HRMS calcd for $C_{18}H_{18}OS$ (M^+) m/z 282.1078, found 282.1099.

5-Fluoro-5,7-dihydro-1,11-dimethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-one (11, Equatorial). To a stirred solution of LDA (1.1 mmol, prepared at 0 °C from methyllithium and diisopropylamine and allowed to stir for 1 h) in THF (2 mL) was added dropwise a solution of **1** (236 mg, 1 mmol) in THF (1 mL) at −78 °C, and then the temperature was raised to 0 °C. After 1 h at 0 °C, the solution was cooled to −78 °C, *N*-fluorodibenzensulfonamide[58] (347 mg, 1 mmol) in THF (1 mL) was added, and stirring was continued for 0.5 h at 0 °C. The ice bath was removed, and the solution was allowed to

(55) That the enhanced reactivity of these equatorial derivatives is greatest for the BF_3-catalyzed reductions rules out chelation as having an important influence on relative rates.

(56) Scholz, D. *Synthesis* **1983**, 944.

(57) The author has deposited the atomic coordinates for the structures **8** and **11** with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(58) Differding, E.; Ofner, H. *Synlett* **1991**, 187.

stir for 1 h at rt. The reaction mixture was quenched with ~1 mL of 0.75 N HCl, concentrated to remove the THF, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product (426 mg) was purified by flash chromatography using Et_2O:hexanes (1:50 v/v) as eluent to afford **11** (117 mg) in 46% yield (unoptimized): mp 108−110 °C; R_f = 0.21 (Et_2O:hexanes, 1:10 v/v); ^{1}H NMR (500 MHz) 7.41−7.25 (m, 5H), 7.11−7.09 (m,1H), 5.76 (d, 1H, J = 47.3 Hz), 3.49 (AB part of ABX, 2H, J = 16.9 and 3.2 (upfield portion) Hz), 2.21 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (125.7 MHz) 203.0, 137.1, 136.8, 135.9, 133.4, 133.3, 133.1, 133.0, 132.4, 130.3, 129.9, 128.2, 128.0, 126.7, 119.8, 119.7, 93.9, 92.4, 46.3, 19.8, 19.4; HRMS calcd for $C_{17}H_{15}FO$ (M^+) m/z 254.1107, found 254.1112.

A suitable sample for X-ray analysis[57] was obtained by recrystallizing **11** from ether−hexanes. An ORTEP plot of **11** appears in the Supporting Information.

5,7-Dihydro-6*H*-dibenzo[*a*,*c*]cyclohepten-6-ol (12). Ketone **1** (51 mg, 0.21 mmol) in THF (4 mL) was treated with an 0.088 M solution of $LiAlH_4$ in THF (0.73 mL, 0.64 mmol). The solution was stirred at 0 °C and quenched with 0.75 N HCl (1 mL) after 2 h. The reaction mixture was concentrated to remove the THF and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum to afford a syrupy product. The crude product was crystallized from ether−hexanes to afford pure **12**: mp 124 °C; ^{1}H NMR (500 MHz) (see Supporting Information) 7.24−7.14 (m, 4H), 7.11−7.05 (m, 2H), 4.26−4.20 (m, 1H), 2.83 (dd, 1H, J = 12.4 and 6.5 Hz), 2.53 (m, 2H), 2.15 (s, 3H), 2.13 (s, 3H), 2.04 (dd, 1H, J = 12.4 and 10.1 Hz); ^{13}C NMR (125.7 MHz) 138.1, 137.9, 137.1, 136.3, 135.8, 135.2, 128.8, 128.7, 127.1, 126.9, 126.6, 125.5, 74.7, 41.2, 40.6, 19.7, 19.7; HRMS calcd for $C_{17}H_{18}O$ (M^+) m/z 238.1358, found 238.1358.

5-Methyl-5,7-dihydro-6*H*-dibenzo[*a*,*c*]cyclohepten-6-ol (13 and 14, Axial Major and Minor). Ketone **2** (100 mg, 0.40 mmol) in Et_2O (2 mL) was treated with LAH (Aldrich, 20 mg, 0.53 mmol). The solution was stirred at rt and quenched with 0.75 N HCl (2 mL) after 1 h. The reaction mixture was concentrated to remove the ether and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum to afford a syrupy product. The crude mixture of alcohols (**13**:**14**, 9:1) was purified by repeated radial silica gel chromatography using Et_2O:hexanes (3:5 v/v) as eluent to afford pure **13** and **14**. Data for **13**: mp 131−132 °C; R_f = 0.21 (Et_2O:hexanes, 1:2 v/v); ^{1}H NMR (300 MHz) 7.21−6.99 (m, 6H), 4.39−4.37 (m, 1H), 3.19 (q, 1H, J = 7.7 Hz), 2.59 (AB part of ABX, 2H, $J_{A,B}$ = 14.0, $J_{A,X}$ = 5.2 (downfield portion), and $J_{B,X}$ = 1.8 (upfield portion) Hz), 2.12 (s, 6H), 0.45 (d, 3H, J = 7.6 Hz); HRMS calcd for $C_{18}H_{20}O$ (M^+) m/z 252.1514, found 252.1528. Data for **14**: R_f = 0.21 (Et_2O:hexanes, 1:2 v/v); ^{1}H NMR (300 MHz) 7.24−6.99 (m, 6H), 3.92−3.87 (m, 1H), 2.86 (q, 1H, J = 7.6 Hz), 2.83 (dd, 1H, J = 12.0 and 5.9 Hz), 2.20 (dd, 1H, J = 12.0 and 10.4 Hz), 2.13 (s, 3H), 2.10 (s, 3H), 0.48 (d, 3H, J = 7.8 Hz); HRMS calcd for $C_{18}H_{20}O$ (M^+) m/z 252.1514, found 252.1519.

The ^{1}H NMR spectra for all major alcohols, the minor methyl axial alcohol, and ketones **1**, **2**, **8**, **9** and **11** appear in Figures 1S−16S of the Supporting Information.

5-Methyl-5,7-dihydro-6*H*-dibenzo[*a*,*c*]cyclohepten-6-ol (Equatorial Major and Minor). Ketone **3** (138 mg, 0.55 mmol) in THF (5 mL) was treated with a 0.10 M solution of $LiAlH_4$ in THF (1.65 mL, 0.17 mmol). The solution was stirred at 0 °C for 15 min. The ice bath was then removed, and the solution was quenched with 0.75 N HCl (1 mL) after 15 min. The reaction mixture was concentrated to remove the THF and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum to afford a syrupy product. The crude mixture of alcohols (major:minor, 6:1) was purified by repeated column chromatography using Et_2O:hexanes (1:50 v/v) as eluent to yield pure major and minor equatorial methyl alcohols. Data for major: mp 127−129 °C; R_f = 0.24 (Et_2O:hexanes, 1:2 v/v); ^{1}H NMR (300 MHz) 7.29−7.04 (m, 6H), 3.99−3.90 (m, 1H), 2.89 (dd, 1H, J = 12.6 and 6.7 Hz), 2.60 (dq, 1H, J = 7.3 and 4.0 Hz), 2.13 (s, 3H), 2.12 (s, 3H), 1.92 (dd, 1H, J = 12.6 and 9.8 Hz), 1.29 (d, 3H, J = 7.3 Hz), 1.00 (d, 1H, J = 8.8 Hz, OH); HRMS calcd for $C_{18}H_{20}O$ (M^+) m/z 252.1514, found 252.1533. Data for minor: mp 114−115 °C; R_f = 0.24 (Et_2O:hexanes, 1:2 v/v); ^{1}H NMR (300 MHz) 7.26−7.05 (m, 6H), 3.65−3.60 (m, 1H), 2.50 (AB part of ABX, 2H, $J_{A,B}$ ~ 13.3, $J_{A,X}$ ~ 3.5 (downfield portion), and $J_{B,X}$ ~ 2.7 (upfield portion) Hz), 2.16 (dq, 1H, J = 9.2 and 6.9 Hz), 2.14 (s, 3H), 2.10 (s, 3H), 1.38 (d, 3H, J = 6.9 Hz); HRMS calcd for $C_{18}H_{20}O$ (M^+) m/z 252.1514, found 252.1512.

5-(Methylthio)-5,7-dihydro-6*H*-dibenzo[*a*,*c*]cyclohepten-6-ol (Axial Major). Compound **8** (25 mg, 0.087 mmol) in THF (4 mL) was treated with a 0.11 M solution of $LiAlH_4$ in THF (0.25 mL, 0.028 mmol). The solution was stirred at 0 °C and quenched with 0.75 N HCl (1 mL) after 2 h. The reaction mixture was concentrated to remove the THF and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum to afford a syrupy product. The crude product was crystallized from ether−hexanes to yield pure major axial methylthio alcohol: mp 218−220 °C; ^{1}H NMR (500 MHz) 7.32−7.08 (m, 6H), 4.47−4.42 (m, 1H), 3.73 (d, 1H, J = 6.9 Hz), 3.40 (d, 1H, J = 11.8 Hz, OH), 2.56 (AB part of ABX, 2H, $J_{A,B}$ = 13.9, $J_{A,X}$ = 5.1 (downfield portion), and $J_{B,X}$ = 1.6 (upfield portion) Hz), 2.13 (s, 3H), 2.12 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (125.7 MHz) 140.5, 138.1, 138.1, 137.4, 137.1, 135.4, 129.7, 128.7, 127.6, 127.1, 126.9, 125.0, 74.8, 61.4, 40.4, 20.8, 19.6, 19.4; HRMS calcd for $C_{18}H_{20}OS$ (M^+) m/z 284.1235, found 284.1231.

5-(Methylthio)-5,7-dihydro-6*H*-dibenzo[*a*,*c*]cyclohepten-6-ol (Equatorial Major). A 6:1 mixture of **9**:**8** (7.1 mg, 0.025 mmol) in THF (4 mL) was treated with $LiAlH_4$ (0.0075 mmol). The solution was stirred at 0 °C and quenched with 0.75 N HCl (1 mL) after 2 h. The reaction mixture was purified by preparative TLC using EtOAc:hexanes (1:20 v/v) as eluent to afford pure major equatorial methylthio alcohol as an oil: R_f = 0.26 (EtOAc:hexanes, 1:5 v/v); ^{1}H NMR (500 MHz) 7.32−7.00 (m, 6H), 4.12−4.07 (m, 1H), 3.51 (d, 1H, J = 3.8 Hz), 2.86 (dd, 1H, J = 12.6 and 6.6 Hz), 2.32 (d, 1H, J = 4.1 Hz, OH), 2.09 (s, 3H), 2.07 (s, 3H), 1.98 (dd, 1H, J = 12.6 and 9.9 Hz); ^{13}C NMR (125.7 MHz) 137.5, 137.4, 137.0, 135.8, 134.4, 129.5, 129.1, 127.4, 127.3, 125.8, 123.9, 74.0, 54.4, 40.2, 19.8, 14.4; HRMS calcd for $C_{18}H_{20}OS$ (M^+) m/z 284.1235, found 284.1247.

5-Methoxy-5,7-dihydro-6*H*-dibenzo[*a*,*c*]cyclohepten-6-ol (Axial Major). Compound **6** (34 mg, 0.13 mmol) in THF (7 mL) was treated with $LiAlH_4$ (0.040 mmol). The solution was stirred at 0 °C and quenched with 0.75 N HCl (1 mL) after 1 h. The reaction mixture was concentrated to remove the THF and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield a syrupy product. The crude product was crystallized from ether−hexanes to afford pure major axial methoxy alcohol: mp 130−132 °C; ^{1}H NMR (500 MHz) 7.32−7.04 (m, 6H), 4.26 (d, 1H, J = 6.0 Hz), 4.23−4.17 (m, 1H), 3.19 (d, 1H, J = 10.1 Hz, OH), 2.87 (s, 3H), 2.55 (AB part of ABX, 2H, $J_{A,B}$ = 14.0, $J_{A,X}$ = 4.8 (downfield portion), and $J_{B,X}$ = 1.6 (upfield portion) Hz), 2.13 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (125.7 MHz) 138.3, 137.6, 137.4, 137.2, 136.4, 135.4, 130.8, 128.4, 127.0, 126.8, 126.5, 126.4, 84.1, 75.8, 56.1, 39.6, 19.5, 19.4; HRMS calcd for $C_{18}H_{20}O_2$ (M^+) m/z 268.1463, found 268.1470.

5-Methoxy-5,7-dihydro-6*H*-[*a*,*c*]cyclohepten-6-ol (Equatorial Major). Compound **7** (68 mg, 0.26 mmol) in THF (8 mL) was treated with $LiAlH_4$ (0.080 mmol). The solution was stirred at 0 °C and quenched with 0.75 N HCl after 1 h. The reaction mixture was concentrated to remove the THF and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum to give a syrupy product. The crude product was purified by column chromatography using EtOAc:hexanes (1:10 v/v) as eluent to afford pure major equatorial methoxy alcohol: mp 95−96 °C; R_f = 0.22 (EtOAc:hexanes, 1:5 v/v); ^{1}H NMR (500 MHz) 7.32−7.05 (m, 6H), 4.30−4.26 (m, 1H), 3.80 (d, 1H, J = 4.5 Hz), 3.38 (s, 3H), 2.83 (dd, 1H, J = 12.6 and 6.8 Hz), 2.44 (d, 1H, J = 2.1 Hz, OH), 2.14 (s, 3H), 2.12 (s, 3H), 2.00 (dd, 1H, J = 12.6 and 10.0 Hz); ^{13}C NMR (125.7 MHz) 137.1, 136.2, 136.0, 135.8, 135.1, 129.3, 129.0, 127.3, 127.1,

125.9, 121.7, 81.0, 74.3, 57.6, 38.5, 19.8, 19.5; HRMS calcd for $C_{18}H_{20}O_2$ (M^+) m/z 268.1463, found 268.1448.

5-Chloro-5,7-dihydro-6*H*-dibenzo[*a*,*c*]cyclohepten-6-ol (Axial Major). A 2:1 mixture of **5**:**4** (33 mg, 0.12 mmol) in THF (2 mL) was treated with $LiAlH_4$ (0.04 mmol). The solution was stirred at 0 °C and quenched with 0.75 N HCl (1 mL) after 1 h. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum to give a syrupy product. The crude product was purified by column chromatography using EtOAc:hexanes (1:5 v/v) as eluent to give pure major axial chloro alcohol: mp 90−91 °C; R_f = 0.28 (EtOAc:hexanes 1:5 v/v); ^{1}H NMR (500 MHz) 7.31−7.08 (m, 6H), 5.18 (d, 1H, J = 6.3 Hz), 4.33−4.30 (m, 1H), 2.65 (AB part of ABX, 2H, $J_{A,B}$ = 14.3, $J_{A,X}$ = 5.4 (downfield portion), and $J_{B,X}$ ~ 0 (upfield portion) Hz), 2.57 (d, 1H, J = 11.7 Hz, OH), 2.16 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (125.7 MHz) 138.4, 138.2, 137.8, 137.1, 136.7, 134.5, 131.3, 129.0, 127.4, 126.9, 126.6, 125.8, 73.5, 67.1, 39.7, 19.7, 19.4; HRMS calcd for $C_{17}H_{17}ClO$ (M^+) m/z 272.0968, found 272.0948.

5-Chloro-5,7-dihydro-6*H*-dibenzo[*a*,*c*]cyclohepten-6-ol (Equatorial Major). To a stirred solution of **5** (54 mg, 0.20 mmol) in THF (5 mL) was added $LiAlH_4$ (0.065 mmol) at 0 °C. After 1 h the reaction mixture was quenched with 0.75 N HCl (1 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum to give a 8.2:1 mixture of major and minor equatorial chloro alcohols. The crude product was purified by column chromatography using EtOAc:hexanes (1:5 v/v) as eluent to afford pure major equatorial chloro alcohol: mp 84−86 °C; R_f = 0.32 (EtOAc:hexanes, 1:5 v/v); ^{1}H NMR (500 MHz) 7.51−7.07 (m, 6H), 4.79 (d, 1H, J = 3.7 Hz), 4.24−4.21 (m, 1H), 2.90 (dd, 1H, J = 12.8 and 6.8 Hz), 2.29 (d, 1H, J = 3.3 Hz, OH), 2.13 (s, 3H), 2.13, (s, 3H), 2.08 (dd, 1H, J = 12.8 and 9.9 Hz); ^{13}C NMR (125.7 MHz): 136.7, 136.6, 135.8, 135.6, 133.3, 130.1, 129.4, 127.7, 127.3, 126.0, 123.7, 76.4, 65.0, 39.5, 19.7, 19.6; HRMS calcd for $C_{17}H_{17}ClO$ (M^+) m/z 272.0968, found 272.0994.

5-Fluoro-5,7-dihydro-6*H*-dibenzo[*a*,*c*]cyclohepten-6-ol (Equatorial Major and Minor). To a stirred solution of **11** (43 mg, 0.17 mmol) in THF (5 mL) was added $LiAlH_4$ (0.051 mmol) at 0 °C. After 1 h the reaction was quenched with 0.75 N HCl (1 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum to give a syrupy product. The crude mixture of alcohols (major:minor, 7.6:1) was purified by preparative TLC using acetone:hexanes (1:10 v/v) as eluent to afford pure major and minor equatorial fluoro alcohols. Data for major equatorial fluoro alcohol: mp 112−114 °C; R_f = 0.35 acetone:hexanes (1:2 v/v); ^{1}H NMR (500 MHz) 7.37−7.09 (m, 6H), 5.12 (dd, 1H, J = 45.6 and 4.5 Hz), 4.48−4.43 (m, 1H), 2.91 (ddd, 1H, J = 12.8, 7.2 and 3.7 Hz), 2.16−2.12 (m, 1H), 2.16 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (125.7 MHz) 136.5, 136.5, 136.4, 135.7, 135.7, 135.2, 133.9, 133.9, 133.8, 133.7, 129.8, 129.3, 127.6, 127.2, 127.2, 126.0, 120.9, 120.8, 93.1, 91.7, 74.2, 74.0, 38.4, 38.3, 19.7, 19.7, 19.3, 19.3; HRMS calcd for $C_{17}H_{17}FO$ (M^+) m/z 256.1263, found 256.1265. Data for minor equatorial fluoro alcohol: R_f = 0.32 acetone:hexanes (1:2 v/v); ^{1}H NMR (500 MHz) 7.39−7.14 (m, 6H), 4.87 (dd, 1H, J = 49.6 and 7.5 Hz), 4.15−4.09 (m, 1H), 2.59 (d, 2H), 2.15 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (125.7 MHz): 136.2, 136.1, 136.0, 135.7, 135.6, 135.3, 134.0, 133.9, 130.0, 129.2, 127.7, 127.2, 127.1, 126.8, 119.6, 119.5, 97.5, 96.1, 78.6, 78.4, 38.2, 38.1, 19.7, 19.3, 19.3; HRMS calcd for $C_{17}H_{17}FO$ (M^+) m/z 256.1263, found 256.1260.

Standardization of LAH Solutions. A mixture of approximately 0.4 mL of a 1.0 M $LiAlH_4$ solution in THF (Aldrich) and 19.6 mL of THF was added to a 25 mL round bottom flask fitted with a septum capped adapter bearing a one-way stopcock. The resulting solution was stirred and sealed with Parafilm. In a separate 10 mL round bottom flask were placed ~40 mg (0.190 mmol) of accurately weighed 1,3-diphenylacetone (Aldrich) and 4 mL of THF. To the 1,3-diphenylacetone solution was added 2 mL of the freshly prepared $LiAlH_4$ solution. The reaction mixture was stirred at rt and quenched with ~1 mL of 0.75N HCl after 2 h. The resulting solution was concentrated *in vacuo* to remove the THF, extracted with $CHCl_3$ (3 × 10 mL), washed with H_2O, and dried over sodium sulfate. The filtered $CHCl_3$ solution was concentrated under reduced pressure and analyzed by either 300 or 500 MHz ^{1}H NMR. The molarity of the $LiAlH_4$ solution was determined by employing the following equation: M of $LiAlH_4$ = $ab/8$, where a = mmol of 1,3-diphenylacetone and b = % of 1,3-diphenylacetone reduced.

Standardization of SBH Solutions. The standardization of sodium borohydride was accomplished as described in the literature with some minor changes.[59] An approximately 16 mg (0.423 mmol) sample of $NaBH_4$ was dissolved in 20 mL of *i*-PrOH and stirred for ~15 min. The solution was then filtered, and a 5 mL aliquot was added to an Erlenmeyer flask containing 25 mL of 0.5 N NaOH. A 0.1500 N solution of KIO_3 was added immediately, and the flask was stirred vigorously. After 30 s, KI (~400 mg) and 20 mL of 4 N H_2SO_4 were then added. The subsequent procedure is identical to that described in ref 59.

General Procedure for the Competitive Reductions by LAH. To a 10 or 25 mL round bottom flask was added the mixture of ketones under study (total ~0.05 mmol) and an appropriate amount of THF to give a final total volume of 4−10 mL of THF (see Appendix 2, Supporting Information). The solution was stirred vigorously at 0 °C for 15 min, ~0.00625 mmol of a standardized solution of $LiAlH_4$ (~0.015 M) was added, and the reaction mixture was quenched after 20 s with ~1 mL of 0.75 N HCl. The resulting solution was diluted with ~20 mL of H_2O, extracted with $CHCl_3$ (5 × 10 mL), and washed with H_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated by careful rotary evaporation (i.e., water bath < 35 °C). The remaining traces of solvent were removed under high vacuum (~25 mT). The oily residue was then analyzed by 500 MHz ^{1}H NMR, and the relative rates were determined as described earlier in Table 2. The 500 MHz ^{1}H NMR spectra for the competitive reduction of the equatorial α-methoxy ketone **7/1** were obtained in benzene-d_6 to remove peak overlap.

As mentioned previously, the decrease in relative rate constants for entries 6 and 8 in Table 1 may be due to incomplete disproportionation and thus involve alkoxyaluminohydride ions. Accordingly, the average from entries 1−5 and 7 was used to calculate $k_{CH_3}^{app}/k_H$. Due to the uncertainty associated with this assumption, we estimate the reliability of the relative rate constant for the axial α-methyl ketone **2** to be ±20%.

For compound **9**, appreciable variation in the rate constant ratio with variation in the ratio of ketones was encountered. Interpretation of this as due to slow disproportionation was supported by observing a large (5-fold) increase in the rate constant ratio when the dialkoxyaluminohydride derived from **1** was used as reducing agent. Only the data from runs 2 and 3 were used. Due to the uncertainty associated with this assumption, we estimate the reliability of $k_{SCH_3}^{ac}/k_H$ to be ±30%. For all remaining substituents this variability was not observed. We estimate the integrals in the ^{1}H NMR spectra to be reliable within 1%. This corresponds to a precision in the relative rate constants of ±5%. The details of individual runs for rate ratio measurements involving all reducing agents appear in Tables 1S−5S of Supporting Information.

General Procedure for the Competitive Reductions by SBH. To a 10 or 25 mL round bottom flask was added the mixture of ketones under study (total ~0.05 mmol) and an appropriate amount of *i*-PrOH to give a final total volume of 4−10 mL (see Appendix 2, Supporting Information). The solution was stirred vigorously at 23 °C for 15 min, ~0.0125 mmol of a standardized solution of $NaBH_4$ (~0.02 M) was added, and the reaction mixture was quenched after 0.75−15 min with ~2 mL of 0.75 N HCl. The resulting solution was diluted with ~20 mL of H_2O, extracted with $CHCl_3$ (5 × 10 mL), and washed with H_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated by careful rotary evaporation (i.e., water bath <35 °C). The remaining traces of solvent were removed under high vacuum (~25 mT). The oily residue was then analyzed by 500 MHz ^{1}H NMR, and the relative rates were determined as described earlier. The 500 MHz ^{1}H NMR spectra for the competitive reduction of the equatorial α-methoxy ketone **7**/**1** were obtained in benzene-d_6

(59) Lyttle, D. A.; Jensen, E. H.; Struck, W. A. *Anal. Chem.* **1952**, *24*, 1843.

to remove peak overlap. We estimate the integrals in the ^{1}H NMR spectra to be reliable within 1%. This corresponds to a precision in the relative rate constants of ±5%.

General Procedure for the Competitive Reductions by Triethylsilane. To a 10 mL round bottom flask was added the mixture of ketones under study (total ~0.05 mmol) and 5 mL of CH_3CN (see Appendix 2 for tabulated details on individual runs). The solution was stirred vigorously at 0 °C, and Et_3SiH (~0.05 mmol, 8.0 μL) was added. After 15 min, $BF_3{\cdot}Et_2O$ (~0.15 mmol, 19 μL) was added, and the solution was quenched after 0.75−16 min with ~2 mL of 0.75 N HCl. The resulting solution was diluted with ~20 mL of H_2O, extracted with $CHCl_3$ (5 × 10 mL), and washed with H_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated by careful rotary evaporation (i.e., water bath <35 °C). The remaining traces of solvent were removed under high vacuum (~25 mT). The oily residue was then analyzed by 500 MHz ^{1}H NMR and the relative rates were determined as described earlier. The 500 MHz ^{1}H NMR, spectra for the competitive reduction of the equatorial α-methoxy ketone **7**/**1** were obtained in benzene-d_6 to remove peak overlap. We estimate the integrals in the ^{1}H NMR spectra to be reliable within 1%. This corresponds to a precision in the relative rate constants of ±5%.

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Supporting Information Available: Tables of individual relative rate constant determinations, ^{1}H NMR spectra of all major reduction products, and ORTEP plots for compounds **8** and **11** (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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