observed. Data are given in Table VIII.

Attempted Equilibration of Enols 3b and 3d. (a) A solution of enol **3b** (20 mg, 0.033 mmol) in dry hexane (25 mL) containing CF_3COOH (1 drop) was refluxed for 72 h. TLC showed no product and after evaporation of the solvent **3b** was recovered. (b) The isomerization experiment starting from **3d** (32 mg) was described above. After reflux for 26 h, **4d** (9.4%) was isolated, and from the chromatography, **3d** (77 mg, 53%) was recovered.

Attempted Enolization of Bis(3-bromo-2,4,6-trimethylphenyl)methyl *tert*-Butyl Ketone. The ketone (18 mg, 0.036 mmol) was dissolved in spectroscopic hexane (10 mL) containing TFA (0.1 mL, 0.001 mmol) and kept at 80 °C. Even after 309 h when TLC showed the presence of six new weak spots, the main spot was that of the ketone and the NMR was identical to that of the ketone. Consequently, no enolization took place.

Crystallographic Parameters. **3a**: $C_{20}H_{20}Br_4O\cdot Et_2O$, M = 670.1, space group C_2/c, a = 33.00 (1) Å, b = 9.151 (4) Å, c = 18.442 (4) Å, β = 112.71 (5)°, V = 5137 (1) Å^3, Z = 8, ρ_{calcd} = 1.73 g cm^{-3}, $\mu(CuK_\alpha)$ = 73.2 cm^{-1}, no. of unique reflections = 3671, no. of reflections with $I \geq 3\sigma_I$ = 3176, R = 0.066, R_w = 0.120, $w^{-1} = \sigma F^2 + 0.006\,836F^2$. **3b**: $C_{21}H_{22}Br_4O\cdot Et_2O$, M = 684.1, space group $P2_1/c$, a = 12.656 (4) Å, b = 10.670 (3) Å, c = 20.684 (5) Å, β = 104.38 (3)°, V = 2705.7 (8) Å^3, Z = 4, ρ_{calcd} = 1.68 g cm^{-3}, $\mu(MoK_\alpha)$ = 58.35 cm^{-1}, no. of unique reflections = 4505, no. of reflections with $I \geq 3\sigma_I$ = 1937, R = 0.070, R_w = 0.077, $w = \sigma F^{-2}$. **3c**: $C_{29}H_{30}Br_4O\cdot MeOH$, M = 746.2, space group $P\bar{1}$, a = 12.935 (5) Å, b = 14.194 (6) Å, c = 9.286 (4) Å, α = 97.96 (2)°, β = 95.38 (2)°, γ = 63.39 (2)°, V = 1508.4 (2) Å^3, Z = 2, ρ_{calcd} = 1.64 g cm^{-3}, $\mu(MoK_\alpha)$ = 52.37 cm^{-1}, no. of unique reflections = 3769, no. of reflections with $I \geq 2\sigma_I$ = 2325, T = 0.066, R_w = 0.067, $w = (\sigma F^2 + 0.000\,139F^2)^{-1}$. **3d**: $C_{24}H_{28}Br_4O$; M = 652.1, space group $P2_1/n$, a = 21.146 Å, b = 12.869 Å, c = 8.944 Å, β = 93.16°, V = 2430.2 Å^3, Z = 4, ρ_{calcd} = 1.78 g cm^{-3}, $\mu(MoK_\alpha)$ = 64.92 cm^{-1}, no. of unique reflections = 3538, no. of reflections with $I \geq 3\sigma_I$ = 2249, R = 0.056, R_w = 0.076, $w^{-1} = \sigma F^2 + 0.004\,657F^2$. **9a**: $C_{24}H_{32}O \cdot 0.5\,CH_2Cl_2$, M = 419.0, space group $P\bar{1}$, a = 13.152 (2) Å, b = 14.522 (2) Å, c = 12.624 (2) Å, α = 112.31 (2)°, β = 97.49 (2)°, γ = 92.59 (2)°, V = 2199.8 (7) Å^3, Z = 4, ρ_{calcd} = 1.14 g cm^{-3}, $\mu(CuK_\alpha)$ = 16.01 cm^{-1}, no. of unique reflections = 5521, no. of reflections with $I \geq 3\sigma_I$ = 4733, R = 0.069, R_w = 0.127. **9d**: $C_{28}H_{40}O$, M = 392.6, space group $P2_1/n$, a = 21.031 (5) Å, b = 12.862 (3) Å, c = 8.762 (3) Å, β = 93.65 (2)°, V = 2365.3 (9) Å^3, Z = 4, ρ_{calcd} = 1.10 g cm^{-3}, $\mu(CuK_\alpha)$ = 4.52 cm^{-1}, no. of unique reflections = 3121, no. of reflections with $I \geq 3\sigma_I$ = 2530, R = 0.070, R_w = 0.116.

X-ray Crystal Structure Analysis. Data were measured on a PW1100/20 Philips Four-Circle Computer-Controlled Diffractometer and on an ENRAF-NONIUS CAD-4 automatic diffractometer for **9**. The method and the calculations[30] (using the SHELXS-86 analysis[30a]) are identical to those described previously.[7b]

Acknowledgment. This work was supported by a grant from the United States-Israel Binational Science Foundation (BSF), Jerusalem, to which we are indebted. I.E. thanks the Absorption Ministry and J.F. thanks the A. Gal Memorial Fund for support. We are indebted to Mr. Michael Gozin for preliminary studies, to Dr. Shmuel Cohen for the X-ray crystallography, to Dr. M. Kaftory for data from the CSDB, and to the Mass Spectrometry Center at the Technion, Haifa, for several mass spectral determinations.

Supplementary Material Available: Tables S1-S30 giving bond lengths, bond angles, and positional, thermal, and structural parameters for **3a-d**, **9a**, and **9d** and Figures S1-S9 giving the ORTEP drawings of **3a-c** and **9a**, stereoscopic views of **3a**, **3b**, **3d**, and **9d**, and the unit cell of **3a** (56 pages); listing of observed and calculated structure factors for **3a-d**, **9a**, and **9d** (106 pages). Ordering information is given on any current masthead page.

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Aldol Additions of Pinacolone Lithium Enolate with Ketones: Reactivities Governed Predominantly by Field Effects

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Abstract: The relative reactivities of representative α- and β-heterosubstituted acyclic, cyclic (five- and six-membered), and aromatic ketones with the lithium enolate of pinacolone in diethyl ether at −78 °C were determined. The order of reactivities of monosubstituted acetones ($MeCOCH_2X$) is X = Cl > OTBDMS > OMe > SMe > NMe_2 > CH_2SMe > H > Me and spans a range of 10^4. Excellent correlation was obtained for $MeCOCH_2X$ when log (k_X/k_{Me}) was plotted against $\sigma_I(X)$ (r = 0.996, ρ = 6.62), demonstrating the overwhelming importance of substituent field/inductive effects in the rate enhancement. Similar linear relationships were also observed for aromatic ketones (r = 0.993, ρ = 7.61) as well as five-membered (r = 0.997, ρ = 6.87) and six-membered ring (r = 0.998, ρ = 6.92) cyclic ketones. Thiacyclopentanone and 3- and 4-thiacyclohexanones were unique among the substrates studied in departing significantly from the correlations shown by all other types of substrates. Similarities of the reactivities for 3-oxacyclohexanone vs cyclohexanone and of 3-oxacyclopentanone vs cyclopentanone to that for methoxyacetone vs butanone established that chelation has no role in the very large rate enhancements observed. The synthetic utility of this effect for regioselective additions was demonstrated by the exclusive addition of pinacolone lithium enolate to the 2-carbonyl in $MeCO(CH_2)_3COCH_2OSiMe_2t$-Bu. Steric retardation by α-methyl and α-methoxy groups was nearly absent in cyclopentanones, small in acyclic ketones, and considerable in cyclohexanones.

Introduction

In sharp contrast to Grignard and organotitanium reagents, the stereochemical results for aldol additions of lithium[1,2] and titanium[3,4] enolates to α- and β-alkoxy aldehydes and ketones indicated that Felkin-Anh transition structures were preferred over chelated ones.[5] The determining factors are not understood, and their elucidation requires knowledge of reactivities. Useful synthetic consequences might well emerge from such studies.

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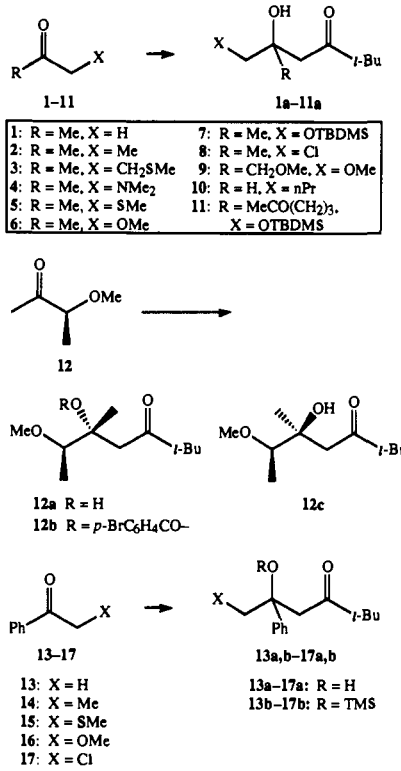
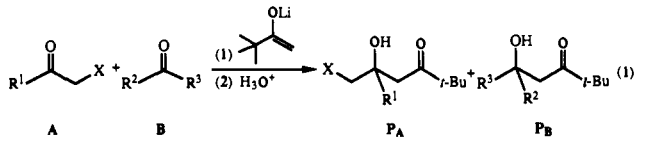
Chart I



Our investigations of these factors have uncovered very large rate accelerations in aldol reactions of α-heterosubstituted aliphatic, aromatic, and alicyclic ketones with the lithium enolate of pinacolone (eq 1). In a preliminary communication[6] we showed that field/inductive effects and not chelation are responsible for

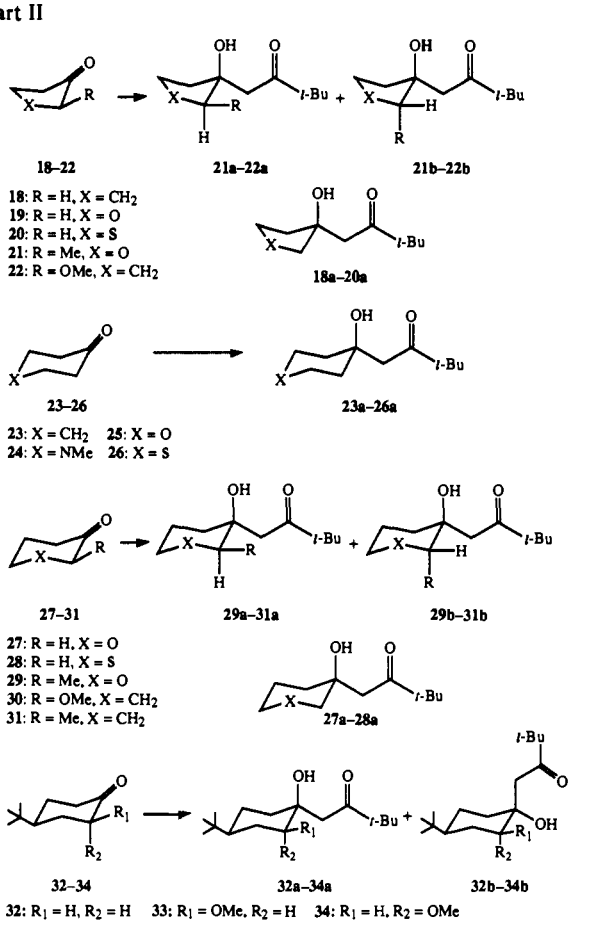


these accelerations. The reactivity differences we have observed are clearly large enough to permit useful intramolecular regioselective and sequential additions to suitably substituted reactants containing more than one keto group. We have now completed a comprehensive set of additional experiments, designed to test our conclusions over a much wider range of substrates. These previously unreported results, presented herein, include data on β-heterosubstituents, the class of aryl alkyl ketones, and α-branched ketones (with the resulting facial selectivities).

Except for the special cases of α-branched and intraring α- and β-thia cyclic ketones, the new results strongly support the conclusion that the field/inductive interaction is the dominant effect upon reactivity. This feature allows us for the first time to evaluate separately the steric effects arising from α-branched substrates.

The role of α and β hetero substituents in additions of organometallic reagents to carbonyl compounds has been the subject of considerable synthetic[1,7] and mechanistic study.[8–12] The chelating ability of α- and β-alkoxy[13] and dialkylamino groups[14]

Chart II



has been exploited in synthesis to dictate the stereochemical outcome in additions of alkylmagnesium and alkyltitanium reagents to carbonyl compounds. Consistent with stereochemical, NMR,[15] solution and solid-state structural,[10,16] and thermodynamic[10] evidence for chelated intermediates, the rates of addition to α- and β-substituted carbonyl compounds are substantially faster than their unsubstituted analogues.[8,9,12,17] Although it was recognized that field/inductive effects do have a role in the rate enhancement, only the importance of chelation in these rate enhancements was emphasized.[12,17] Though lithium-mediated aldol reactions have been the subject of extensive stereochemical, structural, and thermodynamic studies,[18–20] little was known about structural influences on reactivity prior to the present work.[7,21]

Results

The source of the surprisingly large accelerations we found for α-heterosubstituted ketones was unknown but clearly of considerable interest from both mechanistic and synthetic viewpoints. By determining the relative reactivities for a definitive array of structures (Charts I and II), we have now been able to show clearly both the origin of the substituent effect and its structural dependence. Use of competitive kinetics has provided highly reproducible results which we have shown to be largely independent of concentrations of reactants and products. The competition

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Table I. Relative Reactivities for Aldol Reactions of Ketones with Pinacolone Lithium Enolate in Diethyl Ether at −78 °C

entry	ketone pair, (A/B)[b]	relative reactivities, k_A/k_B[a] relay	direct
1	MeCOMe/MeCOEt (1/2)		6.29 ± 0.39[c]
2	$MeCOCH_2CH_2SMe$/MeCOEt (3/2)	9.34 ± 0.67[d,e]	
3	$MeCOCH_2NMe_2$/MeCOEt (4/2)	10.96 ± 0.91[d,e,f]	14.28 ± 0.81[c]
4	$MeCOCH_2SMe$/MeCOEt (5/2)		73.2 ± 2.4[c]
5	$MeCOCH_2OMe$/MeCOEt (6/2)	386 ± 49[c,g] 360 ± 51[c,f,g]	379 ± 27[c]
6	$MeCOCH_2OTBDMS$/MeCOEt (7/2)	943 ± 121[d,g]	718 ± 41[c,e]
7	$MeCOCH_2Cl$/MeCOEt (8/2)	10,711 ± 812[d,g]	
8	$(MeOCH_2)_2CO$/MeCOEt (9/2)	34,704 ± 3,138[d,h]	
9	BuCHO/$(MeOCH_2)_2CO$ (10/9)		3.39 ± 0.23[d]
10	MeCOCH(OMe)Me/MeCOEt (12/2)		30.22 ± 4.03[c]
11	PhCOMe/MeCOEt (13/2)	17.98 ± 2.12[d,e]	
12	PhCOEt/PhCOMe (14/13)		0.57 ± 0.002[d]
13	$PhCOCH_2SMe$/PhCOMe (15/13)		28.6 ± 5.8[c]
14	$PhCOCH_2OMe$/PhCOMe (16/13)		608 ± 10[c]
15	$PhCOCH_2Cl$/PhCOMe (17/13)	8,258 ± 1,817[d,i]	
16	$(CH_2)_4CO$/MeCOEt (18/2)		0.597 ± 0.097[c]
17	THF-3-one/$(CH_2)_4CO$ (19/18)	380 ± 69[d,g]	432 ± 97[c]
18	3-thiacyclopentanone/$(CH_2)_4CO$ (20/18)	661 ± 103[c,j]	
19	2-Me-THF-3-one/$(CH_2)_4CO$ (21/18)		110.9 ± 0.04[d]
20	2-methoxycyclopentanone/$(CH_2)_4CO$ (22/18)	107.8 ± 3.5[d]	
21	$(CH_2)_5CO$/MeCOEt (23/2)	43.3 ± 1.4[d,g]	
22	4-(methylaza)cyclohexanone/$(CH_2)_5CO$ (24/23)		5.37 ± 0.17[d]
23	THP-4-one/$(CH_2)_5CO$ (25/23)		12.7 ± 0.4[d]
24	4-thiacyclohexanone/$(CH_2)_5CO$ (26/23)		70 ± 1[d]
25	THP-3-one/$(CH_2)_5CO$ (27/23)	377 ± 15[d,g]	320 ± 25[d]
26	3-thiacyclohexanone/$(CH_2)_5CO$ (28/23)		34.1 ± 1.6[d]
27	2-Me-THP-3-one/$(CH_2)_5CO$ (29/23)		4.62 ± 0.21[d]
28	2-methoxycyclohexanone/$(CH_2)_5CO$ (30/23)		6.43 ± 1.44[c]
29	2-methylcyclohexanone/$(CH_2)_5CO$ (31/23)		0.0201 ± 0.0018[c]
30	*trans*-4-*t*-Bu-2-MeO-$(CH_2)_5CO$/*cis*-4-*t*-Bu-2-MeO-$(CH_2)_5CO$ (34/33)		2.60 ± 0.10[c]

[a] Errors are reported as standard deviations. [b] $(CH_2)_4CO$ ≡ cyclopentanone, THF ≡ tetrahydrofuran, $(CH_2)_5CO$ ≡ cyclohexanone, THP ≡ tetrahydropyran. [c] Mean of three or more runs. [d] Mean of two runs. [e] $(k_A/k_{MeCOEt}) = (k_A/k_{Me_2CO}) \times (k_{Me_2CO}/k_{MeCOEt})$. [f] Lithium enolate generated from pinacolone trimethylsilyl enol ether + MeLi in Et_2O. [g] $(k_A/k_{MeCOEt}) = (k_A/k_{MeCOCH_2SMe}) \times (k_{MeCOCH_2SMe}/k_{MeCOEt})$. [h] $(k_A/k_{MeCOEt}) = (k_A/k_{MeCOCH_2Cl}) \times (k_{MeCOCH_2Cl}/k_{MeCOCH_2SMe}) \times (k_{MeCOCH_2SMe}/k_{MeCOEt})$. [i] $(k_A/k_{PhCOMe}) = (k_A/k_{PhCOCH_2SMe}) \times (k_{PhCOCH_2SMe}/k_{PhCOMe})$. [j] $(k_A/k_{(CH_2)_4CO}) = (k_A/k_{(CH_2)_5CO}) \times (k_{(CH_2)_5CO}/k_{MeCOEt}) \times (k_{MeCOEt}/k_{(CH_2)_4CO})$.

method avoids complications associated with kinetic analysis of the lithium-mediated aldol reaction,[20] such as uncertainty about the exact nature of the reactive species, fast reaction rates, and the resulting lessened reproducibility.

We have studied the reactions of pinacolone lithium enolate with α- and β-substituted aliphatic, alicyclic, and aromatic ketones and their corresponding unsubstituted analogues. Where relevant, diastereofacial selectivities were determined. Ketones were chosen because their comparatively lower reactivity permits more reliable reactivity measurements. Moreover, cyclic ketones have restricted transition-state conformational possibilities and, when suitably substituted, could serve as experimental models for similar conformations of acyclic ketones. Although pinacolone was chosen for the sake of simplicity (pinacolone lithium enolate is well characterized[18,22]) and because of the small rate of self-condensation, we believe our results are general and probably applicable to lithium enolates of all ketones. Diethyl ether was used as the solvent instead of THF since the lower coordinating ability of the former should make chelated transition structures more likely.

Competitive Rates. Experiments were usually performed using a 5–10-fold molar excess of the two ketones relative to the enolate. Generally, a larger amount of the less reactive ketone was used. The relative rate was calculated using either eq 2 or 3,[23] where P_A and P_B are the final concentrations of the products, and $[A_0]$ and $[B_0]$ are the initial concentrations of the ketones A and B, respectively (cf. eq 1). Equation 2 reduces to eq 3 when $[A_0]$ and $[B_0]$ are large relative to enolate concentration. Unlike eq 2, eq 3 remains valid even when the reactants undergo side reactions. Solubilities at −78 °C did not permit extremely large ketone concentrations; however, the approximation inherent in the 5- to 10-fold excesses used underestimates k_{rel} by no more than 10%. When smaller amounts of more reactive ketone were used, eq 2 was used instead and always gave results which agreed within 10% of that obtained using eq 3. In general, results obtained using higher concentrations of substrates agreed within 10–20% of those obtained using more dilute solutions. Results with lithium enolate generated from the trimethylsilyl enol ether of pinacolone and methyllithium[24] indicate that diisopropylamine has virtually no effect on the relative reactivities (Table I, entries 3 and 5).[20]

$$k_A/k_B = \frac{\ln\{1 - [P_A]/[A_0]\}}{\ln\{1 - [P_B]/[B_0]\}} \quad (2)$$

$$k_A/k_B = \frac{[P_A]/[A_0]}{[P_B]/[B_0]} \quad (3)$$

Product ratios were nearly all determined by capillary GLC; a few were determined by 500 MHz ^1H NMR. Correction factors for determination of molar ratios from GLC peak area ratios were obtained by comparing these numbers with those determined from 500 MHz ^1H NMR spectroscopy. Decomposition and poor line shape in capillary GLC prevented direct assay of aldol products derived from the substituted aromatic ketones; they were therefore converted to their TMS derivatives, which gave clean GLC traces and excellent line shapes.

Aldol reactions of lithium enolates may involve several interconverting, aggregated enolate, enolate–ketone, and enolate–aldolate[25-27] species, all having different reactivities and selectivi-

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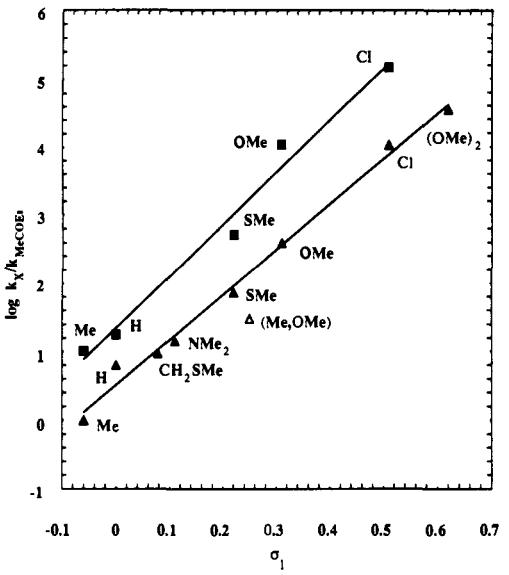

Figure 1. Plot of log (k_X/k_{MeCOEt}) for aldol reactions of ketones with pinacolone lithium enolate in Et_2O at −78 °C, for substituted acetones $MeCOCH_2X$ **1–6**, **8**, and **9** (▲) and acetophenones ($PhCOCH_2X$ **13–17** (■) with respect to butanone, against σ_I. Ratios for acetophenones (Table I) were converted to ratios based on MeCOEt by multiplying each by the constant factor k_{PhCOMe}/k_{MeCOEt} (entry 11). $(OMe)_2$ ≡ 1,3-dimethoxyacetone. (Me,OMe) ≡ 3-methoxybutanone (△); this point was not considered for calculation of the regression equation because of extra steric effects associated with α-branching (see text).

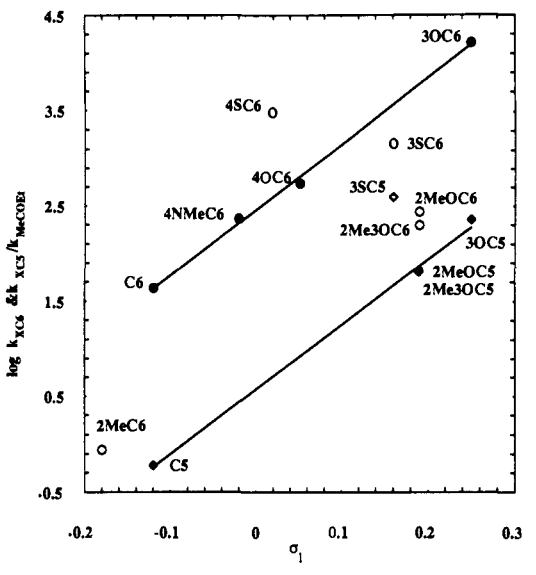

Figure 2. Plot of log (k_{XC6}/k_{MeCOEt}) and log (k_{XC5}/k_{MeCOEt}) for aldol reactions of substituted cyclohexanones (XC6) and cyclopentanones (XC5) with pinacolone lithium enolate in Et_2O at −78 °C, against σ_I. Ratios for cyclic ketones (Table I) were converted to ratios based on MeCOEt by multiplying each by the constant factor $k_{(CH_2)_5CO}/k_{MeCOEt}$ (entry 21) for cyclohexanones or $k_{(CH_2)_4CO}/k_{MeCOEt}$ (entry 16) for cyclopentanones. C6, 4NMeC6, 4OC6, 3OC6 (●) ≡ **23**, **24**, **25**, **27**, respectively. 4SC6, 3SC6, 2Me3OC6, 2MeOC6, 2MeC6 (○), ≡ **26**, **28**, **29**, **30**, **31**, respectively, were not considered in calculation of the regression equation (see text). 3OC5, 2MeOC5, and 2Me3OC5 (overlap), C5 (◆) ≡ 3-oxa-, 2-methoxy-, 2-methyl-3-oxa-, and unsubstituted cyclopentanone, respectively. 3SC5 (◇) ≡ 3-thiacyclopentanone, was not considered in calculation of regression equation (see text).

ties.[18,28] Nevertheless, in *competitive* rate measurements the same enolate species attack both substrates. Consequently, such complicating factors largely cancel, as shown by the very good reproducibility of relative rates obtained using different ratios of the two ketones in each pairwise competition. In a few cases the observed relative reactivities do depend slightly on the relative concentrations of the ketones; lower concentrations tend to improve selectivities. These experiments provide firm evidence that the differences in relative rates are almost exclusively dependent on the characteristics of the ketones rather than on the characteristics of the enolate species. Moreover, in nearly all cases, good agreement of data obtained by direct measurement and by suitable relays using substrates of intermediate reactivity demonstrated that the relative reactivities were not altered substantially by the competing substrates. (Only in the case of relays performed with α-alkoxy ketone substrates did multiplicativity not hold, giving ratios different by up to a factor of 2. The reasons for this are presently under investigation.)

Kinetic Control Experiments. The competition experiment between methoxyacetone and butanone was monitored by GLC over time (5-min intervals) by removing aliquots, followed by standard workup. The product ratio did not change significantly with time although peaks corresponding to self-condensation of the two ketones grew. Self-condensation was probably the result of enolization of the ketone substrates caused by the aldolate rather than deprotonation by the enolate, since very good isolated yields, >75%, were obtained by quenching the reaction after 20–30 min. Equilibration conditions simulated by adding an equivalent amount of LDA under competition reaction conditions to an excess of methoxyacetone, butanone, and a 1:1 mixture of their aldolates followed by standard workup did not lead to any significant change in product ratios. These results demonstrate that the product ratios at −78 °C are indeed kinetically and not thermodynamically controlled.

Relative Reactivities. Results of the competition experiments are given in Table I. Our data show that for both classes of ketones, acyclic (entries 5, 6, and 14), and cyclic (entries 17 and 25) substitution of an α-C–C bond by a C–O bond results in enhancement of reactivity by factors of ca. 400–600. Since the cyclic ketones are geometrically incapable of chelation involving the carbonyl oxygen and the anti-oriented alkoxy oxygen (cf., e.g., **6** vs **19** and **27**), chelation cannot be the major source of rate enhancement. Two methoxy groups make 1,3-dimethoxyacetone react almost as fast as valeraldehyde (entry 9)!

Figure 1 shows that log (k_X/k_{Me}) correlates extremely well with $\sigma_I(X)$[29–31] for all aliphatic (r = 0.996, ρ = 6.62 ± 0.24) and aromatic (r = 0.993, ρ = 7.61 ± 0.60) monosubstituted ketones over a range of more than four orders of magnitude. In the case of cyclic ketones, log k_{rel} was plotted against their composite σ_I

(28) Polt, R.; Seebach, D. *J. Am. Chem. Soc.* **1989**, *111*, 2622–2632.

(29) Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119–251, 171. Though there are more recent σ_I sets which differ somewhat, results are given using the Exner σ_I set because it gives the best correlation. For substituents used here, correlation of the Exner scale with the most recent scale (called σ_F) of Taft is good (r = 0.990; n = 8; F = 311). The main differences are that the Exner scale gives methyl a small negative value and σ_I(MeO) = 0.31, σ_I(MeS) = 0.22, while Taft gives both H and methyl σ_F = 0 and σ_F(MeO) = σ_F(MeS) = 0.25. However, a number of other scales, including those of Grob and of Swain as well as Taft's scale based on ^{19}F NMR chemical shifts, do place the value for MeO greater than that for MeS.[30] These differences probably stem from the fact that the new Taft scale was adjusted using multiple regressions involving σ_F, σ_R, and σ_α. It is not impossible that other scales have small contributions from these effects. The matter is at present uncertain, but since the Exner scale is the best single predictor, its use here is appropriate. We have performed correlations with the other σ_I-type sets[30] as well; all give somewhat higher ρ_I values than the Exner set and somewhat less good fits (r = 0.97–0.98). Thus, no matter which scale is used, the rates are governed predominantly by substituent field/inductive effects. The point for X = *t*-$BuMe_2SiO$ was omitted since σ_I for this substituent could not be found in the literature. As expected, the relative reactivity of this ketone is only slightly greater (ca. 2×) than that of methoxyacetone (X = MeO).

(30) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195. $\sigma_I(XCH_2) = \sigma_I(X)/2.8$ was used to calculate the σ_I values for β substituents.

(31) Assuming (1) additivity of σ_I values and (2) for cyclic ketones, σ_I(–CH_2CH_2–) = $\sigma_I(CH_3)$, σ_I(–CH_2Y–) = $\sigma_I(CH_3Y$–), and σ_I(–CH_2YCH_2–) = $\sigma_I(CH_3YCH_2$–), composite σ_I ($\Sigma\sigma_I$) values are $\Sigma\sigma_I$(1,3-dimethoxyacetone) = $2\sigma_I$(MeO); $\Sigma\sigma_I$(3-methoxy-2-butanone) = σ_I(Me) + σ_I(MeO); $\Sigma\sigma_I$(cyclohexanone, cyclopentanone) = $2\sigma_I$(Me); $\Sigma\sigma_I$(3-oxa- or 3-thiacyclohexanone, 3-oxa- or 3-thiacyclopentanone) = σ_I(Me) + σ_I(MeO/MeS); $\Sigma\sigma_I$(4-oxa, 4-(methylaza), or 4-thiacyclohexanone) = σ_I(Me) + σ_I($MeOCH_2$/Me_2NCH_2/$MeSCH_2$); $\Sigma\sigma_I$(2-methoxycyclohexanone, 2-methyl-3-oxacyclohexanone, 2-methoxycyclopentanone, 2-methyl-3-oxacyclopentanone) = $2\sigma_I$(Me) + σ_I(MeO).

Table II. Diastereofacial Selectivities for Aldol Additions of Ketones with Pinacolone Lithium Enolate in Diethyl Ether at −78 °C

ketone (corresponding diastereomers)	diastereomer ratio
3-MeO-2-butanone (**12a/12c**)[a]	1.14 ± 0.06[b]
c	12.8 ± 1.4[d]
e	0.71 ± 0.02[b]
2-Me-3-oxacyclopentanone (**21a/21b**)[a]	90 ± 2.0[d]
e	80.0 ± 1.3[d]
2-MeO-cyclopentanone (**22a/22b**)[a]	27.8 ± 0.04[d]
e	25.8 ± 0.8[d]
2-Me-3-oxacyclohexanone (**29a/29b**)[a]	10.67 ± 1.52[d]
e	10.3 ± 0.55[d]
2-MeO-cyclohexanone (**30a/30b**)[a]	3.24 ± 0.52[d]
c	69.5 ± 7.0[d]
e	1.05 ± 0.2[d]
f	1.03 ± 0.1[d]
2-Me-cyclohexanone (**31a/31b**)[a]	>100[d,g]
e	>100[d,g]
4-*tert*-butylcyclohexanone (**32a/32b**)[a]	20.7 ± 2.40[d]
cis-4-*tert*-butyl-2-MeO-cyclohexanone (**33a/33b**)[a]	45.7 ± 6[d]
e	*d,g*
trans-4-*tert*-butyl-2-MeO-cyclohexanone (**34a/34b**)[a]	54 ± 13.5[d]
e	*d,g*

[a] Under conditions where an equivalent amount of ketone is injected into the solution of the enolate. [b] Standard deviation of three or more runs. [c] In presence of excess $LiClO_4$. [d] Mean deviation of two runs. [e] In the competition experiment. [f] Enolate added to excess of the ketone. [g] Minor isomer could not be detected.

values,[31,32] and (except for a few cases to be discussed shortly), as seen in Figure 2, very similar correlations were also obtained. Cyclohexanones in general ($r = 0.998$, $\rho = 6.92 \pm 0.24$) react considerably faster than corresponding acyclic ketones and cyclopentanones ($r = 0.997$, $\rho = 6.87 \pm 0.80$), a phenomenon that is well documented for nucleophilic additions to cyclohexanones.[33-35] The reactivity of aromatic ketones lies between those of cyclohexanones and cyclopentanones.

That the dependence of reactivity upon the conformational orientation of an α-alkoxy substituent is relatively small is shown by the observation that *trans*-4-*tert*-butyl-2-methoxycyclohexanone is only 2.6 times more reactive than its cis isomer (entry 30).

The extremely high differences in reactivity of an α-methoxy ketone over an unsubstituted one suggested that highly selective intramolecular aldol additions should be possible. In order to test this assumption, aldol addition to 1-[(*tert*-butyldimethylsilyl)oxy]-2,6-heptanedione (**11**) was examined. Indeed, only the expected adduct, i.e., that resulting from enolate addition to the 2-carbonyl, could be detected by 500 MHz ^{1}H NMR spectroscopy. This result demonstrates the applicability of the high accelerative effect in regioselective synthesis.

A few substrates have been found which do not precisely correlate with the others. Although the monosubstituted acetone series gave excellent correlation with only σ_I (Figure 1), 3-methoxybutanone does not fall on the correlation line. Also, a sulfur atom in the ring always caused departures from linearity—3-thiacyclopentanone is 10× more reactive than predicted by σ_I, and, unexpectedly, 4-thiacyclohexanone is more reactive than 3-thiacyclohexanone! Exocyclically α-substituted cyclohexanones like 2-methyl-, 2-methyl-3-oxa-, and 2-methoxycyclohexanone are considerably less reactive than predicted. While the reactivity pattern of the thiacyclohexanones and thiacyclopentanone is not fully understood, the reactivity of 2-methyl-, 2-methyl-3-oxa-, and 2-methoxycyclohexanone can be analyzed by taking into account the steric bulk of the methyl and methoxy groups (see Discussion).

Diastereofacial Selectivities and Stereochemical Assignments. Table II shows the diastereofacial selectivities for additions to the ketones **12**, **21**, **22**, and **29–34**. Single-crystal X-ray analysis of the *p*-bromobenzoate of one of the two diastereomeric aldol products from 3-methoxy-2-butanone gave the stereochemistry of addition. This substrate was not very selective in diethyl ether or THF. However, in preliminary results, we have found that addition of $LiClO_4$ to ether substantially increases the proportion of Cram cyclic product.

The configuration of the major adduct of 2-methyl-3-oxacyclohexanone was determined by X-ray analysis. At −78 °C, a methyl group is known to provide a very strong conformational bias.[36] Therefore, addition to 2-methyl-3-oxacyclohexanone (and most probably also 3-oxacyclohexanone) is predominantly equatorial. The major isomer exists predominantly in the conformation shown in Chart II (**29a**) and also has a higher R_f compared to the minor product, similar to the results noted[37] for axial cyclohexanols.

The stereochemistry of the major product from 4-*tert*-butylcyclohexanone was confirmed by comparison of the ^{1}H NMR with the chemical shifts reported in the literature.[38] X-ray analysis of the major addition product of *trans*-4-*tert*-butyl-2-methoxycyclohexanone showed that attack was equatorial, indicating that the axial conformation of 2-methoxycyclohexanone should also proceed by equatorial attack to give the *cis*-aldol product. If attack on the cis isomer of 4-*tert*-butyl-2-methoxycyclohexanone were axial, then the equatorial conformation of 2-methoxycyclohexanone should give the cis product. In that case, 2-methoxycyclohexanone should give a very high diastereofacial selectivity favoring the cis product. The low selectivity observed with 2-methoxycyclohexanone is inconsistent with this prediction, showing the predominance of equatorial attack on *cis*-4-*tert*-butyl-2-methoxycyclohexanone. In the case of 2-methoxycyclohexanone, the major product was assigned the stereochemistry shown in Chart II (**30a**), since this product must exist predominantly in the stable conformation shown, and the ^{1}H NMR coupling pattern exhibited by its C(H)OMe proton has one large (axial–axial) coupling (10.9 Hz) and one small coupling (4.3 Hz). Furthermore, its ^{1}H NMR spectrum closely resembles that of the major product of addition to *cis*-4-*tert*-butyl-2-methoxycyclohexanone (**33a**).

As can be seen in Table II, the facial selectivity of 2-methoxycyclohexanone varied somewhat, depending on the solvent and conditions. When the pure ketone was injected into a solution of the enolate, a selectivity of 3.2:1 was found. When the enolate was cannulated into a solution of excess ketone, the selectivity dropped to 1:1, and similar selectivities were obtained in competition experiments with cyclohexanone present.

In preliminary work, we have found a very large increase in facial selectivity for 2-methoxycyclohexanone when the reaction is conducted in the presence of $LiClO_4$ in diethyl ether: from 3:1 to 70:1 in favor of trans addition.

Since in all these cases addition to cyclohexanones is predominantly equatorial (Table II), the major product from 2-methylcyclohexanone (where only one product could be isolated or detected on capillary GLC) is believed to result from equatorial attack (on the most stable conformation) as well. The same mode of attack is believed to be operative with all other cyclohexanones.

The additions of pinacolone lithium enolate to 2-methyl-3-oxacyclopentanone and 2-methoxycyclopentanone are highly selective, and the facial selectivities are similar in competition experiments. The stereochemical assignments for these two ketones are tentative, as the products are liquids at room temperature, and derivatization has not yet produced crystals suitable for X-ray analysis. We believe that since the reactivity is exactly that predicted on the basis of electronic effects alone (Figure 2), the enolate attacks from a direction opposite to the 2-substituent in the cyclopentanone ring.

(32) Cf.: Shorter, J. *Correlation Analysis of Organic Reactivity with Particular Reference to Multiple Regression*; Research Studies Press–Wiley: Chichester, 1982, Chapter 4.
(33) Brown, H. C.; Ichikawa, K. *Tetrahedron* **1957**, *1*, 221–230.
(34) Reetz, M. T.; Hugel, H.; Dresely, K. *Tetrahedron* **1987**, *43*, 109–114, and references therein.
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Discussion

In our investigations on the origins of stereoselectivity in aldol reactions, an important question arose: Why do α-alkoxy-substituted ketones prefer the nonchelation-predicted stereochemistry (i.e., the stereochemistry predicted if the metal is not chelated with the methoxy oxygen) in lithium-mediated aldol reactions, even though chelation-predicted stereochemistry is observed in other organometallic additions? We have discovered that, in *aldol reactions*, α-heteroatom substitution produces high reactivity *entirely in the absence of chelation*—and that, instead, the reactivity is almost completely controlled by the field (σ_I) effect of the α-substituents. Though absence of chelation control might be interpreted to indicate that the chelation pathway has been unexpectedly retarded—e.g., by competing coordination or aggregation of the enolate—our data indicate that the preference for the nonchelation-predicted stereochemistry in these lithium-mediated aldol reactions is primarily associated with *high acceleration of the nonchelation pathway* by the α-alkoxy group.

We have been able to factor out and independently examine the controlling effects not only by the σ_I correlation but also by showing that cyclic ketones containing the α-heteroatom within the ring, conformationally locked out of the range of chelation, give correlations virtually identical to those from open-chain ketones. Cyclopentanones actually give rates which are almost identical to those for corresponding open-chain ketones (cyclohexanones are even more reactive, as has been observed in other reactions of cyclohexanones). For α-chiral-α-alkoxy ketones, our correlations allow us to show that steric retardation caused by α-branching is nearly absent with cyclopentanones and small with acyclic ketones but quite significant with cyclohexanones. We have directly estimated the magnitude of these steric effects by determining reactivities of conformationally restricted cyclohexanones.

Aldol addition to 1-[(*tert*-butyldimethylsilyl)oxy]-2,6-heptanedione (**11**) gave only **11a**, the product of addition to the α-silyloxy carbonyl, revealing a large intramolecular rate acceleration of reaction at the substituted carbonyl group. The reactivity effects shown in Table I indicate that such synthetically useful selectivities should be possible with other substituents as well. Sequential, one-pot reactions can be envisioned, involving a second enolate or a different process at the less reactive carbonyl. Given the magnitude of these reactivity effects, selective reactions involving substrates with *three* different carbonyls, substituted to give low, intermediate, and high reactivity, become plausible.

Origin of Reactivity Effects. A priori, the large rate accelerations caused by α-heterosubstitution of ketones (Table I) might be related to chelation or complex-induced proximity effects,[11,39] orbital overlap factors,[5] electronegativity effects, field/inductive effects, or steric effects. In order to assess the relative contributions of each of these effects and to determine the generality of the structure–activity relationships among various classes of ketones, we measured relative rates for an array of ketone structures and substituents.

Chelation as a source of the rate accelerations can be ruled out on qualitative grounds. Specifically, we find that 3-oxacyclohexanone and 3-oxacyclopentanone, in which the rings constrain the α-oxygens out of the range of chelation, exhibit rate accelerations (relative to cyclohexanone and cyclopentanone, respectively) almost identical to that of acyclic methoxyacetone, demonstrating that chelation cannot be the main source of the rate enhancement (Table I). Also, the strong acceleration produced by a second methoxy group in 1,3-dimethoxyacetone relative to a single one confirms nonchelation, which could only involve one alkoxy group at a time since chelation of lithium to one methoxy group would place it anti to the second methoxy group. Moreover, the order of reactivities does not follow expected complexation order.[10]

It could be argued that in α-heterosubstituted ketones, the increase in reactivity might result from lowering of the energy of the π^* orbital by overlap of the π^* of the C=O and the σ^* orbital of the C–X bond.[5] The magnitude of such lowering is maximal when the C–X bond is orthogonal to the C=O bond, implying considerable angle dependence of the reactivity as well. However, there was no rankwise correlation between the observed reactivity and the π^* orbital energies of the ketones.[40] Moreover, *trans*-4-*tert*-butyl-2-methoxycyclohexanone, **34** (which should have a lower energy LUMO because its geometry permits greater π^*–σ^* mixing), reacts only 2.6 times faster than its cis isomer, **33** (which should have a higher energy LUMO because the σ^* and π^* orbitals are nearly orthogonal). Also, the reactivities of 3-oxacyclopentanone (in which the α-C–O bond is nearly coplanar with the C=O bond[41] and hence lowering of the energy of the π^* orbital is minimal) vs cyclopentanone and of methoxyacetone vs 2-butanone are nearly equal, demonstrating negligible dependence on ability to reach a perpendicular conformation. These observations clearly show that orbital overlap factors (covalent bonding) are not of major importance in stabilizing the transition structure for these aldol reactions. As is apparent from the data, very poor correlation was also obtained when log k_{rel} was plotted against σ_X (group electronegativity)[42] of the substituents.

Instead, we discovered that, for $MeCOCH_2X$, log (k_X/k_{Me}) correlates extremely well with the σ_I (field/inductive parameter) of the substituents X over a range of more than four orders of magnitude (Figures 1 and 2).[29] Similar correlations were found with substituted acetophenones, cyclopentanones, and cyclohexanones as well. The very large ρ values for all these reactions indicate that the rates are overwhelmingly controlled by electrostatic interactions in the low polarity medium diethyl ether. Considering the complexity inherent in lithium enolate aggregation[18,43] and the variety of ketones studied, the excellent correlations obtained in Figures 1 and 2 are gratifying. On closer inspection, it will be seen that certain exceptions can be detected in each series of ketones.

It might be expected that steric effects could influence these reactivities, especially since the enolate nucleophile is relatively bulky and possibly still aggregated in the transition structure. However, the rate correlations with σ_I show that steric effects are minor at best. Still, even relatively small steric effects could have practical consequences in terms of stereo- and regiocontrol. It would therefore be useful to factor out and assess the magnitude of steric effects in the present reactions. The following discussion will assess the relative importance of steric effects in each series.

Substituted Acetones. The relative reactivities of monosubstituted acetones are very highly correlated with σ_I alone [log (k_X/k_{MeCOEt}) = (6.62 ± 0.24)σ_I + 0.51, n = 8, r = 0.996, F = 755].[44] Assuming additivity of σ_I values, the point for 1,3-dimethoxyacetone lies very close to that predicted and hence was included in calculation of the line of best fit. The correlation with σ_I for all monosubstituted aliphatic ketones demonstrates that the field effect alone accounts for greater than 99% of the variation in reactivities. Unsubstituted acetone is a borderline outlier but only by comparison with the extremely close fit of all the monosubstituted acetones.

The steric bulk of the substituents studied varies significantly (as measured, for example, by E_S values). The importance of steric effects was therefore evaluated statistically. Linear multiple regression analyses using steric parameters[45-47] E_S or v in com-

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(41) The calculated O—C—C=O dihedral angle by MACROMODEL 3.1X(MM2) is 176°.

(42) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1–83 (table, p 16).

(43) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737–2769.

(44) Besides the correlation coefficient r, n is the number of data points, and F is the Fisher F statistic. The large F values found here and below are sensitive indicators that these correlations are highly significant. See: Kleinbaum, D. G.; Kupper, L. L.; Muller, K. E. *Applied Regression Analysis and Other Multivariable Methods*, 2nd ed.; PWS-KENT Publishing Co.: Boston, 1988.

(45) Gallo, R. *Prog. Phys. Org. Chem.* **1983**, *14*, 115–163 (table, p 140).

(46) Aslam, M. H.; Burden, A. G.; Chapman, N. B.; Shorter, J.; Charton, M. *J. Chem. Soc., Perkin Trans. 2* **1981**, 500–508.

bination with σ_I all show that there is no significant improvement in the correlation over that given by σ_I alone, i.e., that steric effects are statistically insignificant in explaining the observed substituent effects.

Acetone, in lying above the correlation line for monosubstituted acetones, is more reactive by a factor of 1.9 than predicted by this line ($\sigma_I = 0$ for acetone). A possible reason is that all the monosubstituted acetones have small steric retardations resulting from the bulk of the X group. Variation in this retardation with different X groups could be somewhat masked by the presence of CH_2 between X and the carbonyl. Polarization effects,[48] stabilizing the ketone and partly lost on going to the transition state, might also be involved. On the basis of σ_I substituent effect additivity, 3-methoxy-2-butanone is predicted to react 146 times faster than butanone but is experimentally only 30 times faster. The discrepancy of ca. 4.8 may result from an extra steric effect associated with the conformations available to this α-branched structure. However, such possible steric effects, involving factors of only 2–4, are very small in comparison with the large rate accelerations involved.[45]

Substituted Acetophenones. To show that the results with simple acetones are not fortuitous, we determined reactivities for substituted acetophenones, $PhCOCH_2X$, resulting in a closely similar correlation with σ_I alone [$\log (k_X/k_{MeCOEt}) = (7.61 \pm 0.60)\sigma_I + 1.34$, $n = 5$, $r = 0.993$, $F = 162$]. The fit is excellent, though with somewhat greater scatter than found for the substituted acetones. Since assay of these ratios was best accomplished by GLC analysis of the TMS derivatives of the aldols, the extra scatter probably results from the extra handling and workup. The difference in ρ values between the acetones and acetophenones is not statistically significant. The conclusion is that both series have similar, very high sensitivities to substituent field effects, with little, if any, other contribution.

Substituted Cyclopentanones. The α-carbons in cyclopentanones are held in a nearly staggered conformation with respect to the carbonyl C=O. Our data for cyclopentanones correlate very well with σ_I, giving [$\log (k_{XC5}/k_{MeCOEt}) = (6.87 \pm 0.37)\sigma_I + 0.80$, $n = 4$, $r = 0.997$, $F = 339$ (excluding 3-thiacyclopentanone, **20**, as explained below)]. Significantly, the reactivities of the α-branched ketones 2-methoxycyclopentanone and 2-methyl-3-oxacyclopentanone (111 and 108, respectively, relative to cyclopentanone) lie close to that predicted from field/inductive effects alone (127, based on σ_I additivity). These equalities show that almost no steric/polarization effect is exerted by the methyl or methoxy substituents. Therefore, the preferred stereochemistry of addition (Table II) was tentatively assigned as depicted in Chart II (**21a** and **22a**). A possible reason for the absence of a steric/polarization effect is that the dihedral angles (2-X—C—C=O) in cyclopentanones are considerably greater compared to substituted acetones and especially to cyclohexanones, where one α-substituent nearly eclipses the C=O bond.[49] It is remarkable that the results, even the ρ value (6.87), are so close to those for monosubstituted acetones.

Substituted Cyclohexanones. The data for cyclohexanone together with 4-oxa-, 4-methylaza-, and 3-oxacyclohexanones correlate nicely with σ_I [$\log (k_{3/4\text{-}XC6}/k_{MeCOEt}) = (6.92 \pm 0.24)\sigma_I + 2.46$, $n = 4$, $r = 0.998$, $F = 850$]. This correlation shows that any rehybridization-related ring strain changes[33,34] resulting from α or β heterosubstitution when the substituent is O or N are minimal. Moreover, although cyclohexanones are all uniformly more reactive than open-chain ketones or cyclopentanones, the ρ value (6.92) is very close to that for substituted acetones, again corroborating the similarities among substituted ketones, whether acyclic or cyclic.

The higher conformational rigidity of the cyclohexanones permits approximate factoring of steric effects.[45] 2-Methylcyclohexanone, 2-methyl-3-oxacyclohexanone, and 2-methoxycyclohexanone all react far more slowly (by factors of ~19, ~30, and ~22, respectively) than predicted by their composite σ_I values alone,[50] as calculated from the regression equation. For example, 2-methylcyclohexanone reacts ~50 × more slowly than cyclohexanone. The calculated difference on the basis of the inductive effect of the methyl group is 2.6; consequently, steric/polarization effects may be responsible for a factor of ≈19.

The preferred direction of attack is equatorial in all cyclohexanones. Although the conformational geometries of the α-methyl group in the transition structures are not known, assuming to a first approximation that 2-methyl-3-oxacyclohexanone and 2-methylcyclohexanone have similar steric effects from their respective α-methyl groups, a correction can be made for this effect in the former from the results with the latter. The relative reactivity of 2-methyl-3-oxacyclohexanone calculated by the regression line (139), reduced by the estimated steric/polarization factor of 19, gives a predicted rate of 7.3, which is of similar magnitude to the experimental value (4.6). The agreement is reasonable considering the assumptions made. If a similar steric/polarization effect is assumed for the methoxy group on the basis of the results obtained with the acyclic ketones, the reactivity of 2-methoxycyclohexanone is also predicted to be 7.3 (vs 6.4 observed). It is recognized that the assumed constancy of steric effects for these three 2-substituted cyclohexanones is approximate; however, the approximate constancy can be seen in Figure 2, where a line connecting these three data points (open circles) would have a slope almost parallel to those drawn. Thus, the 2-substituted cyclohexanones appear to be subject to almost exactly the same electrical effects as other species but to react more slowly by an approximately constant factor which is most reasonably assigned as a steric factor resulting from the 2-substitution.

3-Thiacyclopentanone and 3- and 4-Thiacyclohexanones. When cyclic ketones contain sulfur in the ring, in contrast with oxygen, anomalous reactivities are observed (Table I). The origin of these effects is not known with certainty. 3-Thiacyclopentanone reacts about an order of magnitude faster than predicted from field/inductive effects alone. Also, inductive effects alone do not account for the lower reactivity of 3-thiacyclohexanone relative to 4-thiacyclohexanone. There are several instances of abnormal behavior of these ketones in the literature.[51–53] Transannular assistance was proposed to account for acceleration of nucleophilic addition to 4-thiacyclohexanone.[54]

The rate effects may result from the differences in ring strain on rehybridization of the carbonyl carbon, since α-(methylthio)acetone, 2-(methylthio)acetophenone, and 4-(methylthio)-2-butanone all behave normally. However, these acyclic methylthio ketones do deviate if the Taft σ_F values, with $\sigma_F(MeS) = \sigma_F(MeO)$, are used. Consequently, it cannot be ruled out that the sulfur rates, acyclic as well as cyclic, might involve special orbital interactions and not just ring strain effects. Even though our results demonstrate that the rates are controlled predominantly by substituent field/inductive effects, so that sulfur substituent effects must have large field/inductive components, the *deviations* exhibited by sulfur substituents may arise from other effects. Depending on which set of substituent constants is used for correlation, the acyclic methylthio ketone deviations are only ca. 1.5- to 3-fold rate effects (3-fold for Taft σ_F), quite small compared with the observed acceleration effects (Table I).

The high reactivity of 3-thiacyclopentanone, coupled with the high facial selectivities obtained with cyclopentanones, could be

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beneficial in synthesis, as 3-thiacyclopentanone is essentially a masked butanone, while butanone itself is very unreactive and undergoes considerable self-condensation.

Conclusions

We have discovered very high accelerations resulting from α-heterosubstitution of ketones in lithium-mediated aldol condensations. Comparisons of different ketone structures and substituents reveal that the relative reactivities are overwhelmingly governed by the electrostatic field/inductive effects of the substituents and not by chelation or orbital overlap factors. Even though lithium-mediated aldol reactions involve aggregated species and enolate–aldolate complexes are known to dictate stereochemical outcome, rate effects are correlated with the single variable σ_I over a very wide range of reactivities. The same kind of correlation exists for both cyclic and acyclic ketones. Mechanistically, our experiments imply that nonchelation-predicted facial selectivities do not just result from an inefficient chelation mechanism but, rather, a highly accelerated nonchelation mechanism plays a dominant role. The synthetic utility of this effect is shown by a highly regioselective aldol addition to a suitably α-monosubstituted diketone. An α-methyl group exerts a pronounced steric effect when nearly eclipsed to the carbonyl, as in cyclohexanones, but this steric effect is small in substituted acetones and almost absent in cyclopentanones. Anomalous, yet potentially useful, effects, believed to be caused by altered ring geometries, were observed when sulfur was substituted for a methylene in cyclopentanones and cyclohexanones.

Experimental Section

Materials and Methods. All commercially available ketones were dried and/or purified before use by literature methods.[55] Diisopropylamine was distilled from CaH_2. THF and diethyl ether were distilled from sodium/benzophenone ketyl immediately prior to use. Pinacolone was distilled from CaH_2 and stored over 4-Å molecular sieves. Pinacolone trimethylsilyl enol ether was prepared by a previous general procedure for silylation of lithium enolates[56] and purified by distillation under reduced pressure (water aspirator). 4-(Methylthio)-2-butanone (**3**),[57] (methylthio)acetone (**5**),[57] [(*tert*-butyldimethylsilyl)oxy]acetone (**7**),[58] 1,3-dimethoxyacetone (**9**),[59,60] 3-methoxy-2-butanone (**12**),[61] 2-(methylthio)acetophenone (**15**),[57] 3-oxacyclohexanone (**27**),[62-64] 3-thiacyclohexanone (**28**),[65] 2-methyl-3-oxacyclohexanone (**29**),[66-68] and *cis*- and *trans*-4-*tert*-butyl-2-methoxycyclohexanone (**33**, **34**)[69,70] were prepared and purified by literature methods with minor modifications. 3-Oxacyclopentanone (**19**) was prepared by oxidation of commercially available 3-hydroxytetrahydrofuran by pyridinium chlorochromate. 2-Methoxycyclopentanone (**22**) was prepared by treating commercially available cyclopentene oxide with $BF_3{\cdot}OEt_2$ in anhydrous methanol at 0 °C for 10 min and oxidizing the resulting *trans*-2-methoxycyclopentanol with pyridinium chlorochromate.[64,71] $LiClO_4$ was dried under vacuum for 48 h at 100 °C.[72] All reactions and distillations were conducted under argon with oven-dried glassware (160 °C) which was then flame-dried under a stream of argon or under vacuum.

GLC analyses were performed on a Hewlett-Packard 5890 gas chromatograph connected to a HP 3393A integrator, using 25 m Carbowax 20M or phenyl-methyl silicone gum capillary columns. High resolution mass spectra (CI = chemical ionization) were obtained from the University of Pennsylvania Mass Spectrometry Facility of the Chemistry Department, using NH_3 or CH_4 as the carrier gas. Single-crystal X-ray structure determinations were performed by Dr. P. Carroll of the University of Pennsylvania X-ray Crystallography Facility of the Chemistry Department.

Flash column chromatography (FCC) was carried out using the procedure of Still et al.[73] In nearly all cases, the aldol products were conveniently purified by using 80:20 to 70:30 (vol/vol) mixtures of hexanes and ethyl acetate. In case of the very polar (dimethylamino)-acetone adduct, a mixture of dichloromethane, methanol, and concentrated aqueous ammonia was used in the ratio 85:10:5. The relatively nonpolar trimethylsilyl-protected acetophenone adducts were separated using diethyl ether–pentanes 90:10 (vol/vol) mixtures. Rotary evaporation refers to removal of volatile components, including solvent, under water aspirator pressure at ≤30 °C.

General Procedure for Assay of Diastereofacial Selectivity. The procedure for aldol reactions was similar to that of Heathcock et al.[2] Reactions were run in a septum-capped, 25-mL, flame-dried flask under argon. All additions were performed via oven-dried hypodermic syringes or vacuum-dried gas-tight syringes. To diisopropylamine (1.1 mmol, 154 μL) in diethyl ether (5–10 mL) was added *n*-butyllithium (1.1 mmol) in hexanes. After stirring for 10 min at 0 °C, the flask was cooled to −78 °C and stirred for 10 min. Then pinacolone (1.0 mmol, 125 μL) was added dropwise over a period of 15 min. The solution was allowed to stir for 20 min at −78 °C, and then 1.2 mmol of the neat ketone was added. (In the case of solid ketones, the ketone was dissolved in diethyl ether and the solution was added.) The reaction mixture was allowed to stir for 20 min and then quenched by addition of cold water. After warming to ca. 25 °C, the mixture was extracted thrice with diethyl ether. The organics were combined and washed, first with saturated, aqueous $NaHCO_3$ and then with saturated, aqueous NaCl. They were then dried with anhydrous Na_2SO_4 for 15 min, filtered under reduced pressure, and concentrated by careful rotary evaporation. Diastereomer ratios were determined by analytical GLC of the crude diethyl ether solution. For preparative reactions, the reactions were carried out at higher concentrations on a 2- or 3-fold larger scale and were allowed to run for a longer period of time. The diastereomers and other products were then separated and purified by FCC and subjected to spectroscopic and chromatographic analysis. Yields of aldol products varied from ca. 40% (butanone, **2**) to nearly quantitative (1-phenyl-2-methoxyethanone, **16**). Isolated yields (after chromatographic purification) were on the average >65%. No attempt was made to optimize yields.

Trimethylsilyl derivatives of substituted acetophenone-derived aldols were prepared by dissolving the aldol product in anhydrous acetonitrile or dichloromethane, adding excess (5 equiv) of TMS-imidazole, and stirring 12–24 h. Under these conditions, GLC analysis of the crude reaction mixture indicated nearly complete conversion, with less than 2% of the elimination product (enone) being formed, and only occasional traces of the starting material—probably resulting from hydrolytic cleavage during workup. The reaction mixture was quenched with saturated, aqueous $NaHCO_3$ and extracted with diethyl ether. The ether extract was dried with anhydrous Na_2SO_4, concentrated by rotary evaporation, and purified by FCC. Some of these products were quite labile to hydrolysis and gradually hydrolyzed if kept at room temperature over ca. 2 days.

General Procedure for Competition Reactions. The enolate of pinacolone (1 mmol) was generated in diethyl ether (5–10 mL) at −78 °C as described above. (Two experiments were instead conducted by generating the lithium enolate through treatment of the trimethylsilyl enol ether of pinacolone with methyllithium.[24]) This solution was then cannulated into a vigorously stirred mixture of the ketones (ca. 5–10 mmol of each ketone) in diethyl ether (80–200 mL) at −78 °C, and the reaction was allowed to stir for 10–30 min. The reaction mixture was quenched by addition of saturated, aqueous NaCl, extracted thrice with diethyl ether, and dried with anhydrous Na_2SO_4. The solution was concentrated slightly by careful rotary evaporation and analyzed by GLC to determine

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the product ratios. When relatively nonvolatile aldol products were involved, the product ratios were also checked by 500-MHz ^{1}H NMR spectroscopy. In the case of aromatic ketones, all aldol products (except that for acetophenone) decomposed and gave very poor line shapes on attempted GLC analysis. They were therefore converted to their TMS derivatives by the procedure given above. The TMS derivatives gave very clean GLC traces with no decomposition.

Structural Characterizations. Though most of our reactant ketones have previously been reported, almost all of the many aldol adducts which we have isolated are new compounds, fully characterized here for the first time. References are given for previously known substances.

5-Hydroxy-2,2,5-trimethyl-3-hexanone (1a). IR (neat) 3550, 3000, 1700, 1490, 1400, 1360, 1160, 1080, 980 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (s, 1 H), 2.65 (s, 2 H), 1.23 (s, 6 H), 1.14 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.7, 69.6, 46.8, 44.8, 29.3, 26.0; chemical ionization (CI) mass spectrum (MS) (*m/e*) 176.1666 $(M + NH_4)^+$, calcd for $C_9H_{22}NO_2$ 176.1650.[74]

(±)-5-Hydroxy-2,2,5-trimethyl-3-heptanone (2a). IR (neat) 3500, 2968, 2925, 2875, 1685, 1480, 1460, 1390, 1370, 1330, 1280, 1260, 1195, 1150, 1070, 1010, 940, 880, 850, 810, 740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (s, 1 H), 2.64, 2.60 (2d, J = 17.5, 2 H), 1.53, 1.51, (2m, 2 H), 1.16 (s, 3 H), 1.14 (s, 9 H), 0.91 (t, J = 7.5, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 219.1, 71.8, 44.9, 44.8, 34.5, 26.1, 26.0, 8.2. CI MS (*m/e*) 190.1820 $(M + NH_4)^+$, calcd for $C_{10}H_{24}NO_2$ 190.1807.

(±)-5-Hydroxy-2,2,5-trimethyl-7-(methylthio)-3-heptanone (3a). IR (neat) 3477, 2971, 2918, 1692, 1600, 1479, 1485, 1395, 1368, 1330, 1253, 1117, 1068, 1009, 916, 846, 804, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (br s, 1 H), 2.66 (m, 2 H), 2.64–2.50 (m, 2 H), 2.11 (s, 3 H), 1.85–1.81, 1.79–1.70 (2m, 2 H), 1.20 (s, 3 H), 1.14 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.6, 71.3, 45.5, 44.9, 41.4, 28.6, 26.6, 26.0, 15.6; CI MS (*m/e*) 219.1437 $(M + H)^+$, calcd for $C_{11}H_{23}O_2S$ 219.1419.

(±)-5-Hydroxy-2,2,5-trimethyl-6-(*N*,*N*-dimethylamino)-3-hexanone (4a). IR (neat) 3500, 3000, 2900, 2850, 2800, 1700, 1480, 1380, 1060 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44 (br s, 1 H), 2.85, 2.61 (2d, J = 17.5, 2 H), 2.37, 2.34 (2d, J = 13.7, 2 H), 2.30 (s, 6 H), 1.19 (s, 3 H), 1.14 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.4, 72.7, 68.6, 48.0, 44.8, 44.1, 26.4, 26.3; CI MS (*m/e*) 202.1821 $(M + H)^+$, calcd for $C_{11}H_{24}NO_2$ 202.1807.

(±)-5-Hydroxy-2,2,5-trimethyl-6-(methylthio)-3-hexanone (5a). IR (neat) 3484, 2972, 2922, 2873, 1687, 1479, 1465, 1395, 1368, 1334, 1254, 1156, 1113, 1069, 1010, 941, 887, 848, 810, 772, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (s, 1 H), 2.94, 2.67 (2d, J = 17.7, 2 H), 2.74, 2.64 (2d, J = 13.3, 2 H), 2.17 (s, 3 H), 1.28 (s, 3 H), 1.15 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.6, 72.9, 46.1, 44.9, 44.2, 26.9, 26.1, 17.9; CI MS (*m/e*) 205.1239 $(M + H)^+$, calcd for $C_{10}H_{21}O_2S$ 205.1262.

(±)-5-Hydroxy-6-methoxy-2,2,5-trimethyl-3-hexanone (6a). IR (neat) 3489, 2971, 2928, 2872, 2829, 1681, 1479, 1464, 1400, 1330, 1259, 1181, 1110, 1067, 1014, 971, 921, 847, 769 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44 (s, 1 H), 3.35 (s, 3 H), 3.29, 3.23 (2d, J = 9.1, 2 H), 2.88, 2.55 (2d, J = 17.5, 2 H), 1.22 (s, 3 H), 1.14 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.7, 79.4, 71.6, 59.2, 44.8, 42.6, 25.9, 25.2. CI MS (*m/e*) 189.1506 $(M + H)^+$, calcd for $C_{10}H_{21}O_3$ 189.1491.

(±)-6-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-2,2,5-trimethyl-3-hexanone (7a). IR (neat) 3495, 2950, 2925, 2900, 2850, 1680, 1460, 1470, 1410, 1395, 1365, 1260, 1210, 1190, 1100, 1010, 980, 940, 920, 840, 780, 670 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (s, 1 H), 3.50, 3.41 (2d, J = 14.2, 2 H), 2.89, 2.52 (2d, J = 17.6, 2 H), 1.17 (s, 3 H), 1.13 (s, 9 H), 0.89 (s, 9 H), 0.04, 0.03, (2s, 6 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.4, 72.3, 69.5, 44.8, 42.3, 26.1, 25.9, 24.8, 18.2, -5.4, -5.5; CI MS (*m/e*) 289.2203 $(M + H)^+$, calcd for $C_{15}H_{33}O_3Si$ 289.2199.

(±)-6-Chloro-5-hydroxy-2,2,5-trimethyl-3-hexanone (8a). IR (neat) 3475, 2975, 1700, 1480, 1400, 1375, 1340, 1060, 770, 715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.47 (s, 1 H), 3.58, 3.47 (2d, J = 10.9, 2 H), 3.05, 2.61 (2d, J = 17.9, 2 H), 1.31 (s, 3 H), 1.16 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.4, 72.0, 51.0, 44.9, 42.3, 26.1, 25.5; CI MS (*m/e*) 193.1006 $(M + H)^+$, calcd for $C_9H_{18}O_2Cl$ 193.0995.

5-Hydroxy-6-methoxy-5-(methoxymethyl)-2,2-dimethyl-3-hexanone (9a). IR (neat) 3475, 2970, 2950, 2870, 2825, 1700, 1680, 1480, 1460, 1420, 1400, 1370, 1340, 1260, 1180, 1120, 1020, 1070, 980, 930, 860, 800 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.46 (s, 1 H), 3.37, 3.32 (2d, J = 9.5, 4 H), 3.32, (s, 6 H), 2.79 (s, 2 H), 1.43 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.8, 75.9, 73.8, 59.3, 45.0, 38.1, 26.0; CI MS (*m/e*) 219.1572 $(M + H)^+$, calcd for $C_{11}H_{23}O_4$ 219.1596.

(±)-5-Hydroxy-2,2-dimethyl-3-nonanone (10a). IR (neat) 3500, 2970, 2940, 2880, 1705, 1485, 1470, 1400, 1375, 1320, 1280, 1250, 1160, 1080, 1010, 950, 910, 870, 850, 760 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02–3.95 (m, 1 H), 3.22 (d, J = 3.2, 1 H), 2.69 (dd, J = 17.8, 2.5, 1 H), 2.54 (dd, J = 17.8, 9.2, 1 H), 1.56–1.28 (m, 6 H), 1.15 (s, 9 H), 0.91 (t, J = 7.3, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 217.9, 67.8, 44.4, 43.0, 36.1, 27.7, 26.3, 22.7, 14.0; CI MS (*m/e*) 204.1925 $(M + NH_4)^+$, calcd for $C_{11}H_{26}NO_2$ 204.1963.

1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2-methylcyclopentene. 1-Hydroxymethyl-2-methylcyclopentene was prepared and purified by literature methods.[75,76] To a cooled (0 °C) solution of this alcohol (3.105 g, 26.9 mmol) and imidazole (7 g, 103 mmol) in anhydrous DMF (50 mL) was added *tert*-butyldimethylsilyl chloride (8.106 g, 53.8 mmol) in DMF (10 mL). The reaction mixture was allowed to stir for ca. 12 h and then quenched with methanol. The organics were extracted thrice with diethyl ether and washed with saturated, aqueous $NaHCO_3$ and saturated, aqueous NaCl. Concentration by rotary evaporation, followed by removal of the volatile impurities by subjecting the crude product to vacuum (0.5 mmHg) gave essentially a quantitative yield (6.03 g) of the pure product (^{1}H NMR) which was carried over to the next stage (ozonolysis) without further purification. Purification of a small amount by FCC (95:5 pentane–diethyl ether) for spectroscopic characterization yielded a colorless liquid: IR (neat) 2950, 2925, 2850, 1698 (w), 1480, 1470, 1450, 1380, 1360, 1250, 1180, 1090, 1060, 1010, 940, 830, 770 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19 (s, 2 H), 2.43–2.36, 2.33–2.27 (2m, 4 H), 1.77 (qn, J = 7.1, 2 H), 1.65 (s, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 134.5, 133.7, 60.0, 38.9, 34.2, 26.0, 21.5, 18.5, 13.9, -5.3; CI MS (*m/e*) 226.1725 $(M)^+$, calcd for $C_{13}H_{26}OSi$ 226.1753.

1-[(*tert*-Butyldimethylsilyl)oxy]-2,6-heptanedione (11). 1-[(*tert*-Butyldimethylsilyl)oxy]methyl-2-methylcyclopentene (7.231 g, 31.9 mmol), was dissolved in CH_2Cl_2–dry CH_3OH (100 mL, 1:1 vol/vol). The solution was cooled to -78 °C, and ozone was passed into it until a persistant blue color was obtained; the excess ozone was then removed by purging with argon. Excess $(CH_3)_2S$ was added, and the solution was allowed to stir and gradually warm (over 12 h) to ca. 25 °C. The organics were taken up in diethyl ether and washed several times with water. Drying with anhydrous Na_2SO_4, followed by concentration by rotary evaporation and fractional distillation under reduced pressure (bp 100 °C, 0.025 mmHg) yielded the desired diketone **11** (7.01 g, 85%) as a colorless syrup: IR (neat) 2956, 2931, 2896, 2858, 1719, 1473, 1464, 1410, 1362, 1257, 1158, 1105, 1037, 1006, 939, 839, 779 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.12 (s, 2 H), 2.50 (t, J = 7.1, 2 H), 2.45 (t, J = 7.1, 2 H), 2.09 (s, 3 H), 1.82 (qn, J = 7.1, 2 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 210.4, 208.1, 69.2, 42.5, 37.1, 29.8, 25.7, 18.2, 17.1, -5.6; CI MS (*m/e*) 276.2014 $(M + NH_4)^+$, calcd for $C_{13}H_{30}NO_3Si$ 276.1995.

(±)-6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-hydroxy-9,9-dimethyldecane-2,8-dione (11a). IR (neat) 3471, 2956, 2930, 2859, 1716, 1687, 1473, 1470, 1410, 1367, 1258, 1163, 1089, 1007, 939, 837, 778, 670 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.25 (s, 1 H), 3.46 (s, 2 H), 2.90, 2.51 (2d, J = 17.7, 2 H), 2.43 (t, J = 7.3, 2 H), 2.13 (s, 3 H), 1.68–1.62, 1.53–1.44 (2m, 4 H), 1.14 (s, 9 H), 0.88 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.8, 208.9, 73.9, 67.4, 44.9, 44.1, 40.5, 36.5, 29.8, 26.2, 25.8, 18.2, 17.5, -5.5, -5.6; CI MS (*m/e*) 341.2538 $(M - OH)^+$, calcd for $C_{19}H_{37}O_3Si$ 341.2512.

(±)-(5*RS*,6*RS*)-5-Hydroxy-6-methoxy-2,2,5-trimethyl-3-heptanone (12a). IR (CCl_4) 3550, 3000, 2950, 2925, 2900, 2850, 1710, 1480, 1380, 1360, 1340, 1200, 1120, 1080, 1060, 1030, 1020, 875, 865 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 (s, 1 H), 3.35 (s, 3 H), 3.24 (q, J = 6.3, 1 H), 2.76, 2.64 (2d, J = 17.3, 2 H), 1.20 (s, 3 H), 1.15 (d, J = 6.2, 3 H), 1.14 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.6, 82.3, 74.2, 57.2, 45.0, 41.6, 26.1, 24.4, 12.5; CI MS (*m/e*) 185.1535 $(M - OH)^+$, calcd for $C_{11}H_{21}O_2$ 185.1541.

(±)-(5*RS*,6*RS*)-5-[(*p*-Bromobenzoyl)oxy]-6-methoxy-2,2,5-trimethyl-3-heptanone (12b). The *p*-bromobenzoate ester was prepared by minor modification (18 days rather than 18 h reaction time) of a literature method:[2] IR ($CDCl_3$) 3070 (w), 2975, 2925, 2875, 1710, 1590, 1480, 1400, 1290, 1260, 1100, 1010, 1000 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.85 (d, J = 8.5, 2 H), 7.55 (d, J = 8.6, 2 H), 3.88 (q, J = 6.3, 1 H), 3.59, 3.58 (2d, J = 17.9, 2 H), 3.31 (s, 3 H), 1.70 (s, 3 H), 1.27 (d, J = 6.3, 3 H), 1.15 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 213.3, 165.3, 131.6, 131.1, 130.6, 127.8, 86.0, 79.6, 57.2, 44.8, 40.7, 26.5, 21.3, 12.5; CI MS (*m/e*) 385.1285 $(M - OH + NH_4)^+$ [highest *m/e* fragment observable], calcd for $C_{18}H_{28}BrNO_3$ 385.1253. The structure and stereochemistry of **12b** were determined by X-ray analysis (see supplementary material).

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(±)-(5*RS*,6*SR*)-5-Hydroxy-6-methoxy-2,2,5-trimethyl-3-heptanone (12c). IR (neat) 3450, 2975, 2950, 2900, 2875, 2825, 1680, 1475, 1460, 1410, 1390, 1360, 1320, 1250, 1185, 1100, 1070, 1010, 940, 860, 850, 810, 755 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.52 (s, 1 H), 3.30 (s, 3 H), 3.27 (q, J = 6.3, 1 H), 2.99, 2.53 (2d, J = 17.3, 2 H), 1.14 (d, J = 6.1, 3 H), 1.14 (s, 9 H), 1.11 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 219.3, 81.4, 74.0, 56.9, 44.9, 42.4, 26.1, 22.0, 12.5; CI MS (m/e) 185.1532 $(M - OH)^+$, calcd for $C_{11}H_{21}O_2$ 185.1541.

(±)-5-Hydroxy-2,2-dimethyl-5-phenyl-3-hexanone (13a). White, crystalline solid, mp 77–78 °C (lit.[77] mp 75 °C); IR (neat) 3461, 3078, 2979, 2908, 2865, 1674, 1603, 1489, 1475, 1446, 1411, 1397, 1362, 1331, 1276, 1255, 1184, 1156, 1092, 1071, 1049, 1028, 1007, 943, 936, 915, 869, 847, 791, 762, 705, 585, 542 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.25 (m, 5 H), 5.13 (s, 1 H), 3.25, 2.84 (2d, J = 17.5, 2 H), 1.52 (s, 3 H), 1.03 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.2, 147.5, 128.2, 126.6, 124.4, 73.3, 47.4, 44.7, 30.5, 25.8; CI MS (m/e) 238.1779 $(M + NH_4)^+$, calcd for $C_{14}H_{24}NO_2$ 238.1807. The IR spectrum and mp of this compound closely match literature data.[77]

(±)-2,2-Dimethyl-5-[(trimethylsilyl)oxy]-5-phenyl-3-hexanone (13b). IR (neat) 3125, 3100, 3060, 2964, 2920, 2890, 1711, 1605, 1494, 1478, 1447, 1367, 1336, 1251, 1155, 1121, 1074, 1056, 1011, 920, 841, 758, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 7.6, 2 H), 7.29 (t, J = 8.0, 2 H), 7.21 (t, J = 8.0, 1 H), 2.97, 2.85 (2d, J = 15.7, 2 H), 1.89 (s, 3 H), 0.98 (s, 9 H), 0.01 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 213.0, 148.2, 127.8, 126.7, 125.5, 76.8, 51.6, 44.8, 27.4, 26.0, 2.2; CI MS (m/e) 293.1967 $(M + H)^+$, calcd for $C_{17}H_{29}O_2Si$ 293.1937.

(±)-5-Hydroxy-2,2-dimethyl-5-phenyl-3-heptanone (14a). White, crystalline solid, mp 87 °C (lit.[78] mp 89 °C); IR (CCl_4) 3474, 3062, 3027, 2970, 2937, 2880, 1694, 1600, 1494, 1478, 1465, 1448, 1395, 1368, 1324, 1255, 1136, 1112, 1070, 996, 981, 883 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 7.6, 2 H), 7.30 (t, J = 7.4, 2 H), 7.19 (t, J = 7.3, 1 H), 5.04 (s, 1 H), 3.25, 2.79 (2d, J = 17.4, 2 H), 1.85, 1.80 (2m, 2 H), 1.01 (s, 9 H), 0.75 (t, J = 7.4, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.4, 145.8, 128.0, 126.4, 125.1, 75.8, 46.3, 44.7, 35.7, 25.9, 7.6; CI MS (m/e) 235.1726 $(M + H)^+$, calcd for $C_{15}H_{23}O_2$ 235.1698. The IR spectra and mp of this compound closely match literature data.[78]

(±)-2,2-Dimethyl-5-[(trimethylsilyl)oxy]-5-phenyl-3-heptanone (14b). IR (neat) 3060, 3025, 2966, 2885, 1710, 1600, 1495, 1478, 1465, 1447, 1394, 1366, 1340, 1251, 1147, 1109, 1077, 1060, 1029, 920, 892, 839, 756, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2, 2 H), 7.27 (t, J = 7.5, 2 H), 7.19 (m, 1 H), 3.11, 2.99 (2d, J = 16.9, 2 H), 2.32, 2.16 (2dq, J = 14.5, 7.3, 2 H), 0.92 (s, 9 H), 0.85 (t, J = 7.3, 3 H), 0.06 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 212.3, 146.4, 127.7, 126.5, 126.0, 78.9, 48.1, 44.6, 32.1, 26.0, 8.3, 2.3; CI MS (m/e) 291.1761 $(M - CH_3)^+$, calcd for $C_{17}H_{27}O_2Si$ 291.1780.

(±)-5-Hydroxy-2,2-dimethyl-6-(methylthio)-5-phenyl-3-hexanone (15a). Crystalline solid, mp 71 °C; IR (neat) 3463, 3061, 3028, 2971, 2924, 2871, 1691, 1600, 1493, 1478, 1465, 1448, 1395, 1368, 1330, 1241, 1136, 1113, 1073, 1030, 1007, 967, 889 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (m, 2 H), 7.35 (m, 2 H), 7.23 (m, 1 H), 5.09 (s, 1 H), 3.36, 3.18 (2d, J = 17.5, 2 H), 2.93, 2.83 (2d, J = 13.7, 2 H), 2.02 (s, 3 H), 1.04 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.1, 145.3, 128.2, 127.1, 125.0, 76.5, 47.7, 44.8, 44.3, 26.0, 17.6; CI MS (m/e) 267.1402 $(M + H)^+$, calcd for $C_{15}H_{23}O_2S$ 267.1419.

(±)-2,2-Dimethyl-5-[(trimethylsilyl)oxy]-6-(methylthio)-5-phenyl-3-hexanone (15b). IR (neat) 2967, 2915, 2863, 1709, 1600, 1495, 1478, 1447, 1366, 1250, 1055, 1003, 932, 842, 756, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 6.1, 2 H), 7.29 (t, J = 7.2, 2 H), 7.22 (m, 1 H), 3.50, 3.42 (2d, J = 14.4, 2 H), 3.39, 3.26 (2d, J = 17.2, 2 H), 2.07 (s, 3 H), 1.03 (s, 9 H), 0.03 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 212.9, 145.6, 127.9, 127.2, 126.0, 78.8, 46.7, 45.4, 44.7, 26.3, 17.3, 2.3; CI MS (m/e) 323.1472 $(M - CH_3)^+$, calcd for $C_{17}H_{27}O_2SSi$ 323.1501.

(±)-5-Hydroxy-6-methoxy-2,2-dimethyl-5-phenyl-3-hexanone (16a). IR (neat) 3459, 3060, 3025, 2971, 2931, 2826, 1687, 1603, 1495, 1479, 1449, 1408, 1367, 1332, 1256, 1198, 1107, 1073, 1008, 971 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50–7.20 (m, 5 H), 5.09 (s, 1 H), 3.48, 3.46 (2d, J = 9.8, 2 H), 3.38 (s, 3 H), 3.19 (s, 2 H), 1.06 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.2, 144.3, 128.1, 127.1, 125.1, 80.1, 75.5, 59.4, 44.8, 42.4, 26.0; CI MS (m/e) 251.1631 $(M + H)^+$, calcd for $C_{15}H_{23}O_3$ 251.1647.

(±)-6-Methoxy-2,2-dimethyl-5-[(trimethylsilyl)oxy]-5-phenyl-3-hexanone (16b). IR (neat) 3060, 3030, 2950, 2800, 1705, 1600, 1480, 1460, 1370, 1255, 1105, 1080, 1020, 1000, 850, 705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 7.1, 2 H), 7.29 (t, J = 7.4, 2 H), 7.21 (t, J = 7.7, 1 H), 4.02, 3.84 (2d, J = 9.4, 2 H), 3.38 (s, 3 H), 3.11, 2.96 (2d, J = 16.3, 2 H), 0.99 (s, 9 H), 0.04 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 213.0, 145.3, 127.8, 126.9, 125.8, 78.3, 77.0, 58.5, 44.7, 43.7, 26.0, 2.1; CI MS (m/e) 323.2076 $(M + H)^+$, calcd for $C_{18}H_{31}O_3Si$ 323.2042.

(±)-6-Chloro-5-hydroxy-2,2-dimethyl-5-phenyl-3-hexanone (17a). Crystalline solid, mp 56 °C; IR (CCl_4) 3471, 3064, 3030, 2971, 2872, 1696, 1600, 1478, 1449, 1396, 1369, 1331, 1253, 1136, 1112, 1074, 1034, 996 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 8.3, 2 H), 7.35 (t, J = 7.7, 2 H), 7.28 (t, J = 7.6, 1 H), 5.15 (s, 1 H), 3.73, 3.67 (2d, J = 11.5, 2 H), 3.34, 3.22 (2d, J = 17.7, 2 H), 1.07 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 217.7, 143.2, 128.4, 127.7, 125.2, 75.3, 52.9, 44.9, 42.6, 26.0; CI MS (m/e) 272.1433 $(M + NH_4)^+$, calcd for $C_{14}H_{23}NO_2Cl$ 272.1417.

(±)-6-Chloro-2,2-dimethyl-5-[(trimethylsilyl)oxy]-5-phenyl-3-hexanone (17b). IR (neat) 3061, 2966, 2900, 2855, 1710, 1600, 1495, 1478, 1465, 1448, 1395, 1367, 1344, 1251, 1180, 1137, 1087, 1057, 1006, 954, 843, 757, 724, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 7.7, 2 H), 7.31 (t, J = 7.2, 2 H), 7.25 (t, J = 6.3, 1 H), 4.50, 4.10 (2d, J = 11.3, 2 H), 3.27, 3.19 (2d, J = 17.3, 2 H), 1.01 (s, 9 H), 0.07 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 212.5, 143.9, 128.1, 127.5, 125.9, 78.0, 51.6, 46.5, 44.7, 26.1, 2.2; CI MS (m/e) 327.1522 $(M + H)^+$, calcd for $C_{17}H_{28}ClO_2Si$ 327.1547.

1-(1-Hydroxycyclopentyl)-3,3-dimethyl-2-butanone (18a). IR (neat) 3500, 2950, 2860, 1685, 1470, 1460, 1390, 1370, 1320, 1260, 1220, 1170, 1070, 1030, 1000, 960, 890, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.97 (s, 1 H), 2.78 (s, 2 H), 1.87–1.79 (m, 4 H), 1.62–1.55 (m, 2 H), 1.47–1.39 (m, 2 H), 1.15 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 217.8, 80.0, 45.8, 44.5, 39.9, 26.1, 23.8; CI MS (m/e) 185.1531 $(M + H)^+$, calcd for $C_{11}H_{21}O_2$ 185.1541.

(±)-1-(1-Hydroxy-3-oxacyclopentyl)-3,3-dimethyl-2-butanone (19a). IR (neat) 3475, 2960, 2870, 1730 (w), 1690, 1480, 1460, 1440, 1400, 1380, 1280, 1180, 1070, 1050, 1010, 970, 950, 910, 840, 810 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.99 (m, 1 H), 3.95 (s, 1 H), 3.89 (td, J = 8.5, 3.7, 1 H), 3.85 (d, J = 9.4, 1 H), 3.56 (d, J = 9.4, 1 H), 2.97, 2.83 (2d, J = 18.0, 2 H), 2.11 (ddd, J = 12.8, 6.9, 3.6, 1 H), 1.78 (dt, J = 12.9, 8.5, 1 H), 1.16 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 217.9, 78.9, 78.7, 67.4, 44.5, 44.2, 40.1, 26.1; CI MS (m/e) 187.1305 $(M + H)^+$, calcd for $C_{10}H_{19}O_3$ 187.1334.

(±)-1-(1-Hydroxy-3-thiacyclopentyl)-3,3-dimethyl-2-butanone (20a). Crystalline solid, mp 47 °C; IR (CCl_4) 3514, 2971, 2873, 1696, 1479, 1465, 1428, 1396, 1368, 1330, 1289, 1254, 1234, 1197, 1136, 1112, 1084, 1066, 1048, 1008, 956, 889 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.22 (s, 1 H), 3.08 (m, 1 H), 2.98 (d, J = 11.3, 1 H), 2.90, 2.89 (2d, J = 17.2, 2 H), 2.82 (m, 1 H), 2.73 (d, J = 11.3, 1 H), 2.22 (m, 1 H), 1.74 (m, 1 H), 1.16 (s, 9 H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.1, 81.2, 44.7, 43.5, 42.2, 28.6, 26.1; CI MS (m/e) 220.1375 $(M + NH_4)^+$, calcd for $C_{10}H_{22}NO_2S$ 220.1371.

(±)-1-[(1*SR*,2*RS*)-1-Hydroxy-2-methyl-3-oxacyclopentyl]-3,3-dimethyl-2-butanone (21a). IR (neat) 3487, 2973, 2875, 1694, 1480, 1396, 1368, 1244, 1165, 1085, 1032, 979, 941, 893, 862, 673 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.03 (apparent q, $J \approx 7.7$, 1 H), 3.94 (s, 1 H), 3.78 (td, J = 8.7, 4.7, 1 H), 3.56 (q, J = 6.3, 1 H), 2.76, 2.72 (2d, J = 17.7, 2 H), 2.20 (m, 1 H), 1.87 (m, 1 H), 1.21 (d, J = 6.4, 3 H), 1.16 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.0, 81.7, 78.3, 65.2, 44.7, 42.7, 40.1, 26.1, 14.0; CI MS (m/e) 218.1771 $(M + NH_4)^+$, calcd for $C_{11}H_{24}NO_3$ 218.1756.

(±)-1-[(1*SR*,2*SR*)-1-Hydroxy-2-methoxycyclopentyl]-3,3-dimethyl-2-butanone (22a). IR (neat) 3503, 2969, 2873, 2828, 1705, 1479, 1466, 1395, 1366, 1343, 1195, 1114, 1066, 999, 940, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.49 (t, J = 7.7, 1 H), 3.38 (s, 3 H), 2.91, 2.62 (2d, J = 16.9, 2 H), 1.97–1.80, 1.74–1.48 (2m, 6 H), 1.14 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 216.5, 85.9, 76.8, 57.7, 44.4, 43.7, 35.8, 27.3, 26.1, 19.0; CI MS (m/e) 215.1629 $(M + H)^+$, calcd for $C_{12}H_{23}O_3$ 215.1647.

1-(1-Hydroxycyclohexyl)-3,3-dimethyl-2-butanone (23a). White, crystalline solid, mp 59 °C (lit.[79] mp 61–62 °C); IR (CCl_4) 3550, 2960, 2890, 1710, 1500, 1470, 1420, 1390, 1360, 1290, 1200, 1110, 1090, 900, 860 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.30 (s, 1 H), 2.62 (s, 2 H), 1.78–1.20 (m, 10 H), 1.13 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.9, 70.6, 46.0, 44.9, 37.6, 26.0, 25.8, 21.9; CI MS (m/e) 216.1983 $(M + NH_4)^+$, calcd for $C_{12}H_{26}NO_2$ 216.1963. The IR and ^1H NMR spectra of this compound closely match literature data.[79]

1-(4-Aza-1-hydroxy-4-methylcyclohexyl)-3,3-dimethyl-2-butanone (24a). Yellowish white, crystalline solid, mp 63 °C; IR (CCl_4) 3516, 2969, 2940, 2844, 2800, 1696, 1478, 1468, 1449, 1407, 1381, 1368, 1338, 1304, 1279, 1142, 1116, 1077, 1008, 975 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.17 (s, 1 H), 2.61 (s, 2 H), 2.54 (m, 2 H), 2.39 (td, J = 11.7, 2.5, 2 H), 2.29 (s, 3 H), 1.71 (dd, J = 4.0, 2.5, 2 H), 1.55 (td, J = 12.6,

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4.0, 2 H), 1.13 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.8, 68.0, 51.1, 46.3, 46.2, 44.8, 37.1, 25.9; CI MS (*m/e*) 213.1716 $(M)^+$, calcd for $C_{12}H_{23}NO_2$ 213.1729.

1-(1-Hydroxy-4-oxacyclohexyl)-3,3-dimethyl-2-butanone (25a). White, crystalline solid, mp 76 °C; IR (CCl_4) 3509, 2969, 2870, 1696, 1479, 1467, 1405, 1387, 1368, 1337, 1298, 1242, 1118, 1076, 1008, 985, 929 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (s, 1 H), 3.84 (td, *J* = 11.4, 2.9, 2 H), 3.71 (m, 2 H), 2.63 (s, 2 H), 1.62 (m, 2 H), 1.57 (td, *J* = 11.8, 4.5, 2 H), 1.14 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.5, 68.0, 63.5, 46.6, 44.8, 37.6, 25.9; CI MS (*m/e*) 201.1474 $(M + H)^+$, calcd for $C_{11}H_{21}O_3$ 201.1491.

1-(1-Hydroxy-4-thiacyclohexyl)-3,3-dimethyl-2-butanone (26a). White, crystalline solid, mp 69 °C; IR (CCl_4) 3500, 2972, 2934, 2890, 1695, 1478, 1427, 1402, 1368, 1314, 1280, 1218, 1137, 1112, 1066, 937 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (s, 1 H), 3.09 (td, *J* = 13.0, 2.5, 2 H), 2.58 (s, 2 H), 2.34 (dm, *J* = 13.9, 2 H), 1.97 (dm, *J* = 11.8, 2 H), 1.60 (td, *J* = 12.8, 3.5, 2 H), 1.11 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.7, 69.1, 46.8, 44.9, 38.3, 25.9, 23.7; CI MS (*m/e*) 216.1155 $(M)^+$, calcd for $C_{11}H_{20}O_2S$ 216.1184.

(±)-1-(1-Hydroxy-3-oxacyclohexyl)-3,3-dimethyl-2-butanone (27a). IR (neat) 3475, 2975, 2850, 1690, 1480, 1470, 1410, 1400, 1370, 1320, 1210, 1190, 1100, 1070, 1010, 990, 940, 910, 850 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (s, 1 H), 3.67, 3.58 (2m, 2 H), 3.50, 3.39 (2d, *J* = 11.4, 2 H), 2.83, 2.66 (2d, *J* = 17.6, 2 H), 1.80, 1.71, 1.67 (3m, 4 H), 1.15 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.4, 75.1, 68.6, 68.1, 44.9, 41.6, 35.1, 26.0, 23.0; CI MS (*m/e*) 201.1490 $(M + H)^+$, calcd for $C_{11}H_{21}O_3$ 201.1491.

(±)-1-(1-Hydroxy-3-thiacyclohexyl)-3,3-dimethyl-2-butanone (28a). IR (neat) 3490, 2968, 2923, 2855, 1687, 1479, 1465, 1444, 1425, 1395, 1367, 1328, 1283, 1257, 1181, 1144, 1090, 1075, 1059, 1007, 983, 944, 880, 850, 772, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58 (s, 1 H), 3.23, 2.70 (2d, *J* = 17.7, 2 H), 2.70, 2.66 (2d, *J* = 13.8, 2 H), 2.50 (m, 2 H), 2.04 (m, 1 H), 1.83–1.68 (m, 2 H), 1.55 (dt, *J* = 9.8, 2.7, 1 H), 1.16 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.1, 68.8, 44.9, 42.6, 38.1, 37.9, 28.1, 26.1, 25.0; CI MS (*m/e*) 217.1286 $(M + H)^+$, calcd for $C_{11}H_{21}O_2S$ 217.1262.

(±)-1-[(1*SR*,2*RS*)-1-Hydroxy-2-methyl-3-oxacyclohexyl]-3,3-dimethyl-2-butanone (29a). White crystalline solid, mp 50 °C; IR (CCl_4) 3569, 3514 (br), 2970, 2940, 2870, 1709, 1695, 1478, 1463, 1395, 1368, 1347, 1136, 1109, 1070, 996, 966 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 (m, 1 H), 3.69 (s, 1 H), 3.54 (q, *J* = 6.4, 1 H), 3.44 (td, *J* = 11.7, 2.6, 1 H), 2.64, 2.61 (2d, *J* = 17.4, 2 H), 1.99 (qt, *J* = 12.5, 4.6, 1 H), 1.82 (m, 1 H), 1.57 (td, *J* = 13.0, 4.6, 1 H), 1.44 (m, 1 H), 1.16 (d, *J* = 6.4, 3 H), 1.14 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 216.7, 78.0, 70.3, 67.7, 44.9, 42.9, 34.0, 26.0, 22.1, 14.7. The structure and stereochemistry of **29a** were determined by X-ray analysis (see supplementary material).

(±)-1-[(1*SR*,2*SR*)-1-Hydroxy-2-methyl-3-oxacyclohexyl]-3,3-dimethyl-2-butanone (29b). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (s, 1 H), 3.91 (m, 1 H), 3.43 (m, 1 H), 3.31 (q, *J* = 6.4, 1 H), 3.05, 2.51 (2d, *J* = 17.9, 2 H), 2.00 (m, 1 H), 1.70–1.30 (m, 3 H), 1.15 (d, *J* = 6.4, 3 H), 1.17 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 219.8, 80.1, 70.8, 68.2, 45.2, 36.1, 35.7, 26.1, 24.8, 14.9; CI MS (*m/e*) 215.1663 $(M + H)^+$, calcd for $C_{12}H_{23}O_3$ 215.1647.

(±)-1-[(1*SR*,2*SR*)-1-Hydroxy-2-methoxycyclohexyl]-3,3-dimethyl-2-butanone (30a). IR (neat) 3460, 2936, 2865, 2822, 1698, 1479, 1464, 1443, 1415, 1393, 1365, 1351, 1308, 1265, 1195, 1145, 1103, 1010, 982, 954, 932, 889, 854 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 (s, 1 H), 3.33 (s, 3 H), 3.07 (dd, *J* = 10.9, 4.3, 1 H), 2.92, 2.60 (2d, *J* = 17.5, 2 H), 1.95–1.15 (m, 8 H), 1.14 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 217.9, 83.1, 73.4, 56.3, 44.9, 43.3, 36.2, 26.1, 24.7, 20.8; CI MS (*m/e*) 229.1807 $(M + H)^+$, calcd for $C_{13}H_{25}O_3$ 229.1804.

(±)-1-[(1*SR*,2*RS*)-1-Hydroxy-2-methoxycyclohexyl]-3,3-dimethyl-2-butanone (30b). White solid, mp 60 °C; IR (neat) 3475, 2990, 2925, 2855, 2825, 1680, 1465, 1440, 1360, 1320, 1250, 1190, 1030, 1010, 970, 945, 920, 880, 845, 800, 750 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.74 (s, 1 H), 3.29 (s, 3 H), 3.17 (dd, *J* = 5.8, 2.6, 1 H), 2.98, 2.48 (2d, *J* = 17.5, 2 H), 1.95–1.18 (m, 8 H), 1.14 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 219.9, 81.6, 73.2, 56.6, 45.0, 41.0, 34.4, 26.1, 24.0, 21.3, 20.5; CI MS (*m/e*) 229.1786 $(M + H)^+$, calcd for $C_{13}H_{25}O_3$ 229.1804.

(±)-1-[(1*SR*,2*SR*)-1-Hydroxy-2-methylcyclohexyl]-3,3-dimethyl-2-butanone (31a). IR (neat) 3491, 2970, 2934, 2858, 1690, 1480, 1462, 1395, 1368, 1345, 1316, 1260, 1211, 1170, 1151, 1069, 1013, 984, 893, 844, 786, 712 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.1 (br s, 1 H), 2.65 (m, 2 H), 1.78–1.62 (m, 3 H), 1.53–1.31 (m, 3 H), 1.28–1.08 (m, 3 H), 1.13 (s, 9 H), 0.92 (d, *J* = 10.8, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 219.9, 72.6, 45.1, 44.3, 40.1, 37.0, 30.2, 25.9, 25.7, 21.6, 15.6; CI MS (*m/e*) 213.1863 $(M + H)^+$, calcd for $C_{13}H_{25}O_2$ 213.1854.

1-(1-Hydroxy-*t*-4-*tert*-butylcyclohexyl)-*r*-3,3-dimethyl-2-butanone (32a). IR (CCl_4) 3475, 2957, 2872, 1681, 1475, 1432, 1418, 1390, 1369, 1326, 1298, 1255, 1234, 1198, 1177, 1156, 1071, 1021, 986, 964, 929, 886, 844, 830, 801, 773, 730, 652, 603, 553 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.09 (s, 1 H), 2.56 (s, 2 H), 1.85–1.75, 1.60–0.85 (2m, 9 H), 1.13 (s, 9 H), 0.86 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 219.1, 70.0, 48.0, 47.3, 44.8, 37.8, 32.4, 27.6, 25.9, 22.1; CI MS (*m/e*) 255.2329 $(M + H)^+$, calcd for $C_{16}H_{31}O_2$ 255.2324. The ^{1}H NMR spectrum of this compound closely matches literature data.[38]

1-(1-Hydroxy-*c*-4-*tert*-butylcyclohexyl)-*r*-3,3-dimethyl-2-butanone (32b). ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.68 (s, 1 H), 2.74 (s, 2 H), 1.9–1.65, 1.58–1.40, 1.10–0.85 (3m, 9 H), 1.15 (s, 9 H), 0.86 (s, 9 H). The ^{1}H NMR spectrum of this compound closely matches literature data.[38]

(±)-1-[(1*SR*,2*SR*,4*SR*)-1-Hydroxy-2-methoxy-4-*tert*-butylcyclohexyl]-3,3-dimethyl-2-butanone (33a). IR (neat) 3450 (br), 2935, 2860, 1695, 1475, 1460, 1440, 1240, 1120, 1100, 1020, 980, 940 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.83 (s, 1 H), 3.35 (s, 3 H), 3.08 (dd, *J* = 11.4, 4.3, 1 H), 2.92, 2.59 (2d, *J* = 17.1, 2 H), 2.00–1.88, 1.50–1.20, 1.10–0.90 (3m, 7 H), 1.13 (s, 9 H), 0.88 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 218.0, 83.9, 72.9, 56.5, 46.4, 44.9, 43.3, 35.9, 32.5, 27.6, 26.1, 25.7, 21.6; CI MS (*m/e*) 285.2447 $(M + H)^+$, calcd for $C_{17}H_{33}O_3$ 285.2430.

(±)-1-[(1*SR*,2*RS*,4*SR*)-1-Hydroxy-2-methoxy-4-*tert*-butylcyclohexyl]-3,3-dimethyl-2-butanone (34a). Solid, mp 73 °C; IR (CCl_4) 3490, 2950, 2860, 2825, 1690, 1480, 1460, 1415, 1390, 1360, 1320, 1220, 860, 840 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.47 (s, 1 H), 3.27 (m, 1 H), 3.22 (s, 3 H), 2.99, 2.40 (2d, *J* = 17.7, 2 H), 1.95–1.85, 1.60–0.95 (2m, 7 H), 1.14 (s, 9 H), 0.86 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 220.1, 80.7, 71.8, 55.7, 44.9, 42.9, 40.2, 33.9, 32.0, 27.4, 26.0, 23.5, 21.5; CI MS (*m/e*) 285.2400 $(M + H)^+$, calcd for $C_{17}H_{33}O_3$ 285.2430. The structure of **34a** was determined by X-ray analysis (see supplementary material).

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Supplementary Material Available: X-ray determination data, ORTEP diagrams, and tables of refined atomic positional and thermal parameters for the X-ray structures of **12b**, **29a**, and **34a** (17 pages). Ordering information is given on any current masthead page.