Acyclic Stereoselection. 17. Simple Diastereoselection in the Addition of Medium- and Long-Chain *n*-Alkyl Ketone Lithium Enolates to Aldehydes[1]

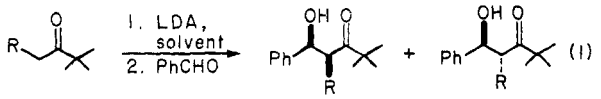
Clayton H. Heathcock* and John Lampe

Department of Chemistry, University of California, Berkeley, California 94720

Received February 1, 1983

The *n*-alkyl *tert*-butyl ketones **1b–d** have been prepared and the stereochemistry of their aldol reaction with benzaldehyde has been investigated. As with ketone **1a**, ketones **1b–d** give *Z* enolates that react with benzaldehyde in THF at −78 °C to give syn aldols. When the aldol additions are carried out in pentane, the syn aldols are also the kinetic products, but syn–anti equilibration is much more rapid in this solvent; after reaction at 25 °C for 20 min, ketones **1c** and **1d** give only the anti aldols **3c** and **3d**. Aldolate syn–anti equilibration becomes more facile as the size of the α-alkyl group increases. Ketone **14** has been prepared and employed in a synthesis of methyl (±)-isocorynomycolate; the crucial aldol addition, leading to β-hydroxy ketones **15** and **16**, proceeds with kinetic stereoselection of only 4.5:1.

As part of our general program aimed at understanding the stereochemistry of the reaction of preformed lithium enolates with aldehydes,[2,3] we found that the *Z* enolate of ethyl *tert*-butyl ketone (**1a**) reacts with various aldehydes to give syn aldols (**2a**).[4–6] To further explore the scope of this relationship, we have examined the reactions of *n*-alkyl *tert*-butyl ketones **1b–d** with benzaldehyde (eq 1).

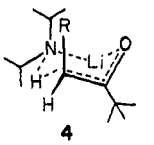


1 **2** **3**

a: R = Me, **b**: R = Et, **c**: R = *n*-Pr, **d**: R = *n*-Bu

In this paper, we report the results of this study, which turned up some interesting information with regard to steric effects on the rate of deprotonation of ketones by lithium diisopropylamide (LDA) and to solvent effects on the rate of stereomutation of diastereomeric aldolates.

Ketones **1a–d** were converted into their lithium enolates by treatment with LDA in THF at −78 °C or in pentane at 25 °C.[9] Preliminary experiments revealed that there is a steric effect on the rate of the deprotonation reaction. Whereas ketone **1a** (0.2 M in THF) is completely deprotonated by LDA in 20 min at −78 °C,[4] compound **1d** requires 4 h at the same temperature for complete deprotonation. For ketones **1b** and **1c**, we carried out the enolate-formation step for 2 h in THF at −78 °C, with good results. This steric retardation of the enolization process is consistent with Ireland's model (**4**)[10] in which it is clear



4

that increasing bulk in R should have the observed effect.

Aldol condensations were carried out by addition of benzaldehyde to the enolate solution; the reaction was quenched after 10–20 min by the addition of aqueous ammonium chloride. Data are summarized in Table I. As shown in Table I, condensations of ketones **1a–d** in THF at −78 °C uniformly give the syn aldols **2a–d** (entries 1, 4, 6, 8). The kinetic stereoselectivity of **1b–d** is estimated by ^{1}H NMR and ^{13}C NMR spectroscopy of the unpurified products to be >98.2%. Reaction of ketone **1a** in pentane at −78 °C also gives only the syn aldol (entry 2). However, the condensations in pentane at 25 °C give substantial amounts of anti aldols **3a–d** (entries 3, 5, 7, 9). It is interesting to note that the syn:anti ratio decreases as the chain length of R increases; with ketones **1c** and **1d**, no syn aldol is detected after a reaction time of 20 min.

The data in Table I clearly show that the observed differences in stereoselectivity are due to syn–anti equilibration, rather than to a solvent effect on the stereochemistry of the deprotonation process (cf. entries 10 and 11) or to a solvent effect on the kinetic stereoselectivity of the addition reaction (cf. entries 2 and 12). Comparison of entries 12 and 13 is particularly enlightening in this regard. It has previously been determined that the lithium aldolates corresponding to **2a** and **3a** equilibrate with a half-life in ether of approximately 8 h.[4] In the current study, we determined that the same equilibration proceeds in pentane at 25 °C with a half-life of 45 min. As the size of R increases, the rate of syn–anti equilibration also increases.[11] Although exact half-lives were not determined for R = Et, *n*-Pr, and *n*-Bu, the data in Table I allow one to estimate that $t_{1/2}^{25}$ for the equilibrium **2b** ⇄ **3b** is about 7 min while those for **2c** ⇄ **3c** and **2d** ⇄ **3d** are less than 4 min. Indeed, the data in entry 12 may indicate that some equilibration occurs in this case even at −78 °C.

An explanation for the observed solvent effect on the rate of syn–anti equilibrium is suggested in the partial

(1) For part 16, see C. H. Heathcock and L. A. Flippin, *J. Am. Chem. Soc.*, **105**, 1667 (1983).
(2) C. H. Heathcock, *Science*, **214**, 395 (1981).
(3) C. H. Heathcock in "Asymmetric Synthesis," J. D. Morrison, Ed., Academic Press, New York, 1983, Vol. 3.
(4) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).
(5) Although only one enantiomer is depicted in each case, all structures in this paper represent racemates.
(6) Several recent papers[7] have pointed out problems with the traditional use of erythro and threo for the nomenclature of diastereomers such as **2** and **3** (see ref 2, inter alia). As a result, we now have no fewer than *three* new systems for systematic nomenclature of such isomers. However, it is still convenient to have a simple convention for describing the relative configuration of two asymmetric carbons, such that the relationship between reaction topography and product stereostructure may be described without the confusion that often results from the use of stereostructural descriptors that change with trivial changes of structure. In this and succeeding papers, we shall employ the Masamune syn–anti system[8] for this purpose.
(7) (a) D. Seebach and V. Prelog, *Angew. Chem., Int. Edn. Engl.*, **21**, 654 (1982); (b) F. A. Carey and M. E. Kuehne, *J. Org. Chem.*, **47**, 3811 (1982); (c) J. H. Brewster, *ibid.*, submitted for publication.
(8) S. Masamune, Sk. A. Ali, D. L. Snitman, and D. S. Garvey, *Angew. Chem., Int. End. Engl.*, **19**, 557 (1980).
(9) H. O. House, W. V. Phillips, T. S. B. Sayer, and C.-C. Yau, *J. Org. Chem.*, **43**, 700 (1978).
(10) (a) R. E. Ireland and A. K. Willard, *Tetrahedron Lett.*, 3975 (1975); (b) R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
(11) J. Mulzer, M. Zippel, G. Brüntrup, J. Segner, and J. Finke, *Liebigs Ann. Chem.*, 1108 (1980).

0022-3263/83/1948-4330$01.50/0

Table I. Diastereomeric Ratios in the Reactions of Ketones 1a-d with Benzaldehyde (Eq 1)

entry	ketone	enolization solvent	reaction solvent	reaction temp, °C	reaction time, min	diastereomer ratio, 2:3
1	1a	THF	THF	−78	10	98.7:1.3[a]
2	1a	pentane	pentane	−78	20	>98:2
3	1a	pentane	pentane	25	15	80:20
4	1b	THF	THF	−78	10	>98:2
5	1b	pentane	pentane	25	20	15:85
6	1c	THF	THF	−78	10	>98:2
7	1c	pentane	pentane	25	20	<5:95
8	1d	THF	THF	−78	10	>98:2
9	1d	pentane	pentane	25	20	<5:95
10	1d	pentane	THF	−78	15	>98:2
11	1d	THF	pentane	25	300	<2:98
12	1d	pentane	pentane	−78	15	90:10
13	1d	pentane	pentane	−78 → 25	30	<2:98

[a] See ref 4, footnote 36.

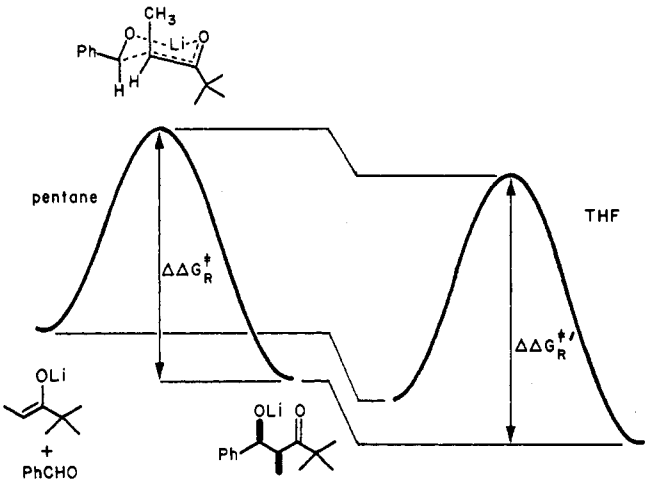


Figure 1. Energy profile for the reaction of the *Z* enolate of ketone **1a** with benzaldehyde in pentane and THF.

reaction coordinate diagram shown in Figure 1. The basic tenet of this proposal is that negative charge is more delocalized in the transition state for the addition reaction than it is in either the reactants or the products of the reaction. Thus, the reactants and products of the reaction will be stabilized more on changing from a less polar to a more polar solvent than will the transition state. It follows that both the aldol addition reaction and its reversal should be more rapid in pentane than in THF.

The foregoing argument treats the lithium enolate, the lithium aldolate, and the aldol transition state as monomeric species. This is almost certainly an oversimplification. It has been shown by Jackman that lithium enolates exist primarily as tetramers in ether or THF.[12] The proposed structure of the lithium enolate tetramer[12,13] is in striking agreement with the X-ray crystal structures of recently isolated THF solvates of the lithium enolates of pinacolone and cyclopentanone.[14] Of course, it is possible that an enolate may exist principally in an aggregated form in solution, yet react as a monomer. Such a phenomenon is, in fact, precedented by the behavior of methyllithium, which exists as a tetramer both in solution and in the solid state, but reacts as a monomer.[15] Alternatively, the tetrameric lithium enolate may react as such, in which case an aldehyde molecule may replace a solvent ligand from one lithium of the enolate tetramer and the ensuing adduct may undergo subsequent aldol addition (Figure 2). Three more cycles of this process would convert the enolate tetramer into an aldolate tetramer. Whatever the intimate details of the mechanism, the arguments regarding charge delocalization should still apply, and the conclusion that pentane and other nonpolar solvents should accelerate aldol reversal would seem to be valid.

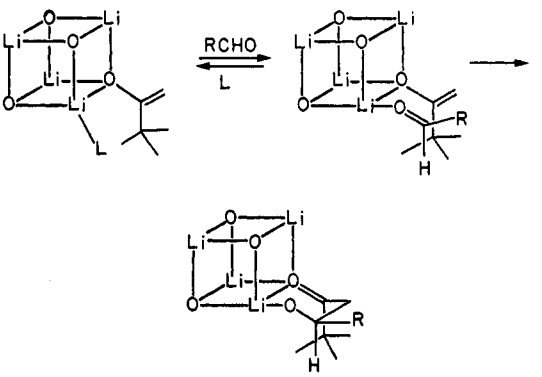


Figure 2. Possible mechanism for aldol addition reactions of enolate tetramers (only one ligand and one enolate are shown for clarity).

Table II. ^{13}C NMR Chemical Shifts for Aldols 2 and 3[a]

entry	R	syn isomer, 2 C-1	syn isomer, 2 carbinol	anti isomer, 3 C-1′	anti isomer, 3 carbinol
1	CH_3[b]	12.2	74.0	16.5	77.5
2	C_2H_5	20.0	73.4	23.4	74.6
3	n-C_3H_7	28.8	73.4	32.5	74.7
4	n-C_4H_9	26.6	73.6	29.4	74.3

[a] Chemical shifts expressed in ppm downfield of Me_4Si. [b] Data taken from ref 17.

In connection with the foregoing studies, it was necessary to rigorously assign stereostructures to aldols **2b–d** and **3b–d**. Several criteria were employed. First, it was found that the vicinal coupling constants, $J_{1,2}$, are smaller in the isomers produced in THF (4–5 Hz) than in those formed in pentane (6–7 Hz).[16] It has also been shown that ^{13}C NMR spectroscopy may be used to assign stereostructures to β-hydroxy-α-methyl carbonyl compounds.[17] Exami-

(12) (a) L. M. Jackman and N. M. Szeverenyi, *J. Am. Chem. Soc.*, **99**, 4954 (1977); (b) L. M. Jackman and B. C. Lange, *Tetrahedron*, **33**, 2737 (1977).

(13) H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971).

(14) (a) R. Amstutz, W. B. Schweizer, D. Seebach, and J. D. Dunitz, *Helv. Chim. Acta*, **64**, 2617 (1981); (b) D. Seebach and J. Golinski, *ibid.* **64**, 1413 (1981).

(15) S. G. Smith, L. F. Charbonneau, D. P. Novak, and T. L. Brown, *J. Am. Chem. Soc.*, **94**, 7059 (1972).

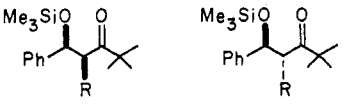
(16) (a) M. Stiles, R. R. Winkler, Y. Chang, and L. Traynor, *ibid.*, **86**, 3337 (1964); (b) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *ibid.*, **95**, 3310 (1973).

Table III. ^{1}H NMR *tert*-Butyl Chemical Shifts for Compounds 5 and 6[a]

entry	R	5	6
1	CH_3[b]	0.77	1.35
2	C_2H_5	0.79	1.33
3	n-C_3H_7	0.78	1.19
4	n-C_4H_9	0.77	1.27

[a] Chemical shifts expressed in ppm downfield from Me_4Si. [b] Data for compounds 5a and 6a taken from ref 4 and 18.

nation of the spectra of compounds **2b–d** and **3b–d** reveals that this criterion may be used in this series of compounds. The most useful resonances are those of the carbinol carbon and the methylene carbon (C-1′) directly attached to the main chain of the molecule, both of which are shifted to higher field in the syn isomer than in the anti isomer (Table II). Finally, the silylated aldols **5a–d** and **6a–d**

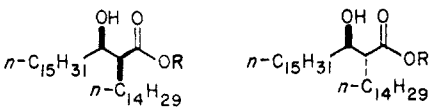


5 **6**

a: R = Me, **b**: R = Et, **c**: R = *n*-Pr, **d**: R = *n*-Bu

were prepared and their ^{1}H NMR spectra obtained. Silylated aldols **5a–d** are easily prepared by quenching the aldol condensation reaction mixture in THF with trimethylsilyl chloride. Attempts to apply this method to condensations carried out in pentane lead only to complex product mixtures containing small amounts of **6a–d**. However, the anti silylated aldols are readily prepared by silylation of aldols **3a–d** with *N,O*-bis(trimethylsilyl)acetamide or with *N*-(trimethylsilyl)imidazole. The *tert*-butyl resonances in the ^{1}H NMR spectra of syn isomers **5a–d** occur at substantially higher field than those of the corresponding anti isomers **6a–d** (Table III). The difference presumably stems from the shielding effect of the aromatic ring on the *tert*-butyl group in the favored conformer for the syn isomer, as shown in Figure 3.

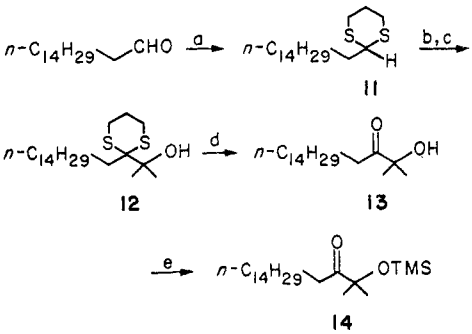
Isocorynomycolic acid (**7**) is the syn diastereomer of corynomycolic acid (**8**), the simplest example of an inter-



7: R = H **8**: R = H
9: R = Me **10**: R = Me

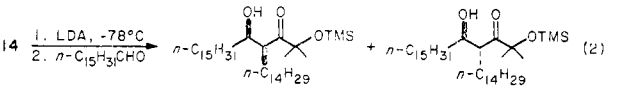
esting group of natural β-hydroxy acids known as mycolic acids, the esters of which with trehalose are called "cord factors".[19] We have previously reported a stereoselective synthesis of (±)-**8** and its methyl ester, **10**.[20] In connection with the current study, we have carried out a synthesis of (±)-**9**. As a reagent for a projected syn-selective aldol addition, we prepared ketone **14**, as shown in Scheme I; the overall yield for the four-step sequence is 37%. Ketone **14** was treated with LDA in THF at −78 °C and palmit-

Scheme I[a]



[a] a, $HS(CH_2)_3SH$, BF_3·Et_2O; b, n-C_4H_9Li, −20 °C; c, acetone, −78 °C; d, $HgCl_2$, $CaCO_3$, CH_3CN, H_2O; e, BSA.

aldehyde was added to the resulting enolate solution. As expected from our experience with ketones **1b–d**, formation of the lithium enolate **14** is relatively difficult; the yield of aldol product is only 10% when the enolization time is 45 min and 40% when the enolization time is 4 h (both 0.5 M). However, when an enolization time of 9 h is employed, the yield of aldol is 60%; the ratio of syn and anti aldols **15** and **16** under these conditions is 82:18 (eq 2).



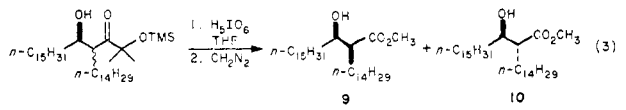
15 **16**

Very high yields of aldol products may be obtained if, in addition to using a long enolization time, one allows the addition reaction to proceed at an elevated temperature; however, the stereoselectivity of the process suffers somewhat under these conditions. For example, with an enolization time of 10.5 h and a reaction time of 30 min at −78 °C, followed by 30 min at 0 °C, the yield of aldol is 80%, but the **15**:**16** ratio is only 75:25.

The aldols **15** and **16** proved to be sensitive to retroaldolization and could not be chromatographed without the loss of significant amounts of material. The crude aldol mixture was therefore converted directly without purification into the corresponding mixture of the methyl esters **9** and **10**. The aldol diastereomer ratios were determined by chromatographic analysis of this mixture of esters, since the aldol diastereomers **15** and **16** could not be differentiated by the use of any of the available techniques. There is some danger that preferential reaction of one diastereomer during the conversion of the aldol mixture to the methyl esters could cause the syn:anti ratio of the esters to differ from that of the original aldol mixture. For this reason, the diastereomer ratios obtained can only be viewed as being an approximate indication of the stereoselectivity of the aldol condensation.

The oxidative cleavage of aldols **15** and **16** to give the corresponding hydroxy acids proved to be more difficult than had been anticipated. Cleavage reactions of this type are generally carried out with periodic acid in mixtures of methanol and water,[4] but the limited solubility of aldols **15** and **16** in such solvent mixtures renders these conditions ineffective in the present case. However, a solution of periodic acid in tetrahydrofuran[21] proved to be particularly effective. Treatment of the mixed aldols with a THF solution of periodic acid for 6 h followed by esterification with diazomethane provides the mixed esters in yields of 72–75%, as shown in eq 3. In contrast to the mixture of diastereomeric β-hydroxy ketones **15** and **16**, esters **9** and

(17) C. H. Heathcock, M. C. Pirrung, and J. E. Sohn, *J. Org. Chem.*, *44*, 4294 (1979).
(18) W. A. Kleschick, Ph.D. Dissertation, University of California, Berkeley, 1976.
(19) For reviews on the chemistry and biological properties of mycolic acids and cord factors see: (a) E. Lederer, *Chem. Phys. Lipids*, **16**, 91 (1976); (b) E. Lederer, A. Adain, R. Ciorbaru, J. F. Petit, and J. Wietzerbin, *Mol. Cell. Biochem.*, **7**, 87 (1975).
(20) C. H. Heathcock, M. C. Pirrung, S. H. Montgomery, and J. Lampe, *Tetrahedron*, **37**, 4087 (1981).
(21) R. E. Ireland and J. Newbould, *J. Org. Chem.*, **28**, 23 (1963).

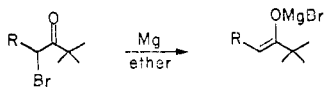


(3)

9 10

10 are easily separable by chromatography on silica gel, albeit with some retroaldolization to give methyl palmitate and palmitaldehyde.

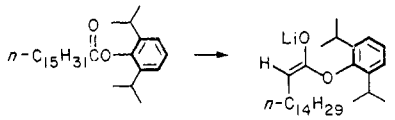
Although the foregoing synthesis demonstrates that stereoselective aldol technology may be employed for the synthesis of β-hydroxy carbonyl compounds having a long-chain *n*-alkyl group, rather than a methyl group, at the α position, the observed stereoselectivity (**15**:**16** = 4.5:1) is disappointingly low. One might be inclined to assume, on the basis of the results obtained with ketones **1b–d**, that the low stereochemical yield observed in the reaction of ketone **14** is due to partial equilibration. However, the stereochemical outcome is essentially independent of the reaction time at −78 °C. As mentioned earlier, when the reaction proceeds for 30 min at −78 °C and 30 min at 0 °C the **15**:**16** ratio falls to 75:25. This result presumably reflects partial equilibration. If we assume, as is generally the case with aldols such as **2–3** or **15–16**, that the anti isomer is significantly more stable than the syn isomer, then little equilibration can occur in 30 min at 0 °C. It follows that the degree of equilibration at −78 °C must be negligible. Thus, it seems that the kinetic stereoselectivity of the enolate of ketone **14** is simply lower than expected. Dubois has shown that the kinetic stereoselectivity of *Z* enolates derived from ketones **17a–d** is a function of the



17

a: R = Me, b: R = Et, c: R = *i*-Pr, d: R = *t*-Bu

steric bulk of R.[22] It may be that *n*-alkyl groups of medium length (i.e., compounds **1b–d**) behave as "small" groups, but that the long-chain alkyl group of **14** coils back upon itself so that its effective steric bulk is increased.[23] Finally, it should be noted that the previously reported synthesis of methyl (±)-corynomycolate (**10**), which employed the anti-selective reagent **18**, also proceeds in low



18 19

stereochemical yield, in this case only 68%.[20] Since compound **18** presumably reacts by way of its *E* enolate, **19**,[24] the lower stereochemical yield is expected; it has previously been shown that *Z* enolates display higher kinetic stereoselectivity than do *E* enolates.[4,22]

In summary, the research reported in this paper demonstrates that *n*-alkyl *tert*-alkyl ketones may be used as syn-selective reagents for aldol additions. Stereoselectivity is excellent for *n*-alkyl chains of modest length. With the single compound studied having a truly long-chain *n*-alkyl substituent, syn:anti selectivity is disappointingly low. in such a case, the extra effort entailed in preparing the necessary reagent is not justified if the diastereomeric products can easily be separated chromatographically, as is the case with β-hydroxy esters **9** and **10**.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Ether and tetrahydrofuran (THF) were distilled from sodium benzophenone immediately prior to use. All reactions involving organometallic reagents were conducted under a nitrogen atmosphere. Boiling points and melting points (pyrex capillary) are uncorrected. IR spectra were determined with a Perkin-Elmer Model 297 infrared recording spectrophotometer. ^{1}H NMR spectra were determined on the following spectrometers: Varian T-60, Varian EM 390, UCB 200, or UCB 250 (super-conducting, FT instruments operating at 200 and 250 mHz, respectively). ^{13}C NMR spectra were measured at 25.14 MHz with a Nicolet TT-23 spectrometer, at 50.31 MHz on the UCB 200, or at 62.89 MHz on the UCB 250. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are tabulated in order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) in hertz. Mass spectra were obtained with Atlas MS-12 and Consolidated 12-110B mass spectrometers. Mass spectral data are tabulated as *m*/*e* (intensity expressed as percent of total ion current). Gas–liquid partition chromatography (GLC) was done with Varian Aerograph A-90P, 920, and 940 gas chromatographs. High-performance liquid chromatography (HPLC) was done with a Waters Model ALC/GPC-244 liquid chromatograph (analytical) or a Waters PrepLC/system 500 (preparative). Columns used were μPorasil unless otherwise indicated. Elemental analyses were performed by the Microanalytical Laboratory operated by the College of Chemistry, University of California, Berkeley, CA.

2,2-Dimethyl-3-hexanol. A solution of 2.65 mL (2.15 g, 28.6 mmol) of butyraldehyde in 20 mL of ether was cooled to −78 °C, and 16.5 mL (32.5 mmol) of a 1.97 M solution of *tert*-butyllithium in pentane was added over a 30-min period. The solution was stirred at −78 °C for 1 h and allowed to warm to room temperature. The reaction mixture was stirred for 2.5 h at room temperature and poured into 75 mL of saturated aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted twice with ether. The combined organic phases were washed with 10% aqueous $NaHSO_3$ and water and were dried ($MgSO_4$). Evaporation of the solvent provided 3.42 g (92%) of the alcohol as a clear colorless liquid: IR (film) 3400, 1460, 1360, 1110, 1070, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (9 H, s), 0.93 (3 H, t, *J* = 7), 1.08–1.70 (4 H, m), 3.15 (1 H, m). Preparative GLC (8% SE-30, 10 ft × 0.25 in., 140 °C) showed that this material was 95% pure, and an analytical sample was collected. Anal. Calcd for $C_8H_{18}O$: C, 73.78; H, 13.93. Found: C, 74.04; H, 13.89.

2,2-Dimethyl-3-heptanol. A solution of 3.26 mL (2.58 g, 30.0 mmol) of pivaldehyde in 30 mL of ether was cooled to −78 °C, and 24.5 mL (32.8 mmol) of a 1.34 M solution of *n*-butyllithium in hexane was added over a 30-min period. The solution was stirred at −78 °C for 1 h and allowed to warm to room temperature. The reaction mixture was stirred for 2.5 h at room temperature and poured into 75 mL of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted twice with ether. The combined organic phases were washed with 10% aqueous $NaHSO_3$ and water and dried ($MgSO_4$). Evaporation of the solvent provided 4.20 g (97%) of the alcohol as a pale yellow liquid: IR (film) 3400, 1460, 1360, 1110, 1070, 1000 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.77–1.07 (3 H, m), 0.87 (9 H, s), 1.07–1.67 (6 H, m), 3.12 (1 H, m). Preparative GLC (8% SE-30, 10 ft × 0.25 in., 160 °C) showed that this material was 95% pure, and an analytical sample was collected. Anal. Calcd for $C_9H_{20}O$: C, 74.94; H, 13.97. Found: C, 75.03; H, 13.79.

2,2-Dimethyl-3-octanol. A solution of 2.40 mL (2.00 g, 20.0 mmol) of hexanal in 20 mL of ether was cooled to −78 °C, and 10.1 mL (19.9 mmol) of a 1.97 M solution of *tert*-butyllithium in pentane was added over a 10-min period. The solution was stirred at −78 °C for 1 h and allowed to warm to room temperature. The reaction mixture was stirred for 2.5 h at room temperature,

(22) P. Fellmann and J. E. Dubois, *Tetrahedron*, **34**, 1349 (1978).
(23) H. A. Smith and J. P. McReynolds, *J. Am. Chem. Soc.*, **61**, 1963 (1939).
(24) To avoid confusion associated with variation of the metal counterion, when discussing enolates of esters, the OM ligand is assigned priority over the OR ligand in assigning *E* or *Z* stereochemical notation, regardless of the nature of M and R.[25]
(25) D. A. Evans in "Asymmetric Synthesis," J. D. Morrison, Ed., Academic Press, New York, 1983, Vol. 3.

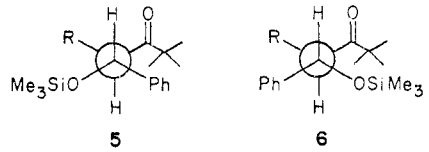


Figure 3. Preferred conformations for compounds **5** and **6** where **a**, R = Me; **b**, R = Et; **c**, R = *n*-Pr; **d**, R = *n*-Bu.

and poured into 75 mL of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted twice with ether. The combined organic phases were washed with 10% aqueous $NaHSO_3$ and water and dried ($MgSO_4$). Evaporation of the solvent provided 2.86 g (91%) of the alcohol as a clear colorless liquid: IR (film) 3380, 1460, 1360, 1110, 1080, 1000, 940, 930 cm^{-1}; ^1H NMR (CCl_4) δ 0.77–1.03 (3 H, m), 0.87 (9 H, s), 1.03–1.66 (8 H, m), 1.97 (1 H, br s), 3.05 (1 H, m). Preparative GLC (10% SE-30, 10 ft × 0.25 in., 200 °C) showed that this material was greater than 95% pure, and an analytical sample was collected. Anal. Calcd for $C_{10}H_{22}O$: C, 75.88; H, 14.01. Found: C, 76.01; H, 13.87.

General Procedure for the Preparation of Ketones 1b–d. Preparation of 2,2-Dimethyl-3-hexanone (1b). The following procedure illustrates the preparation of ketones **1b–d**. A solution of 3.41 g (26.1 mmol) of 2,2-dimethyl-3-hexanol in 50 mL of CH_2Cl_2 was added to a rapidly stirring suspension of pyridinium chlorochromate[26] in 50 mL of CH_2Cl_2. The mixture was stirred for 11 h, after which the solvent was decanted from the mixture and the residue was triturated 3 times with ether. The combined solvents were evaporated and the residue was distilled to give 1.33 g (40%) of the desired ketone as a yellow liquid: bp 112–113 °C [lit.[22] bp 145 °C (738 torr)]; IR (film) 1700, 1460, 1360, 1110, 1060, 1000 cm^{-1}; ^1H NMR ($CDCl)_3$ δ 0.88 (3 H, t, J = 7), 1.13 (9 H, s), 1.57 (2 H, sextet, J = 7), 2.43 (2 H, t, J = 7). Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.67; H, 12.48.

2,2-Dimethyl-3-heptanone (1c). Oxidation of 4.14 g (28.7 mmol) of 2,2-dimethyl-3-heptanol using the general procedure followed by distillation of the crude product gave 3.07 g (75%) of the desired ketone as a clear colorless liquid; bp 149–150 °C [lit.[27] bp 166 °C (745 torr)]; IR (film) 1700, 1480, 1360, 1120, 1060, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 6), 1.13 (9 H, s), 1.20–1.72 (4 H, m), 2.47 (2 H, t, J = 7). Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.76. Found: C, 76.16; H, 12.67.

2,2-Dimethyl-3-octanone (1d). Oxidation of 2.63 g (16.7 mmol) of 2,2-dimethyl-3-octanol using the general procedure followed by distillation of the crude product afforded 1.41 g (54%) of the desired ketone as a yellow liquid: bp 80 °C (20 torr) [lit.[27] bp 184–185 °C (745 torr)]; IR (film) 1700, 1480, 1360, 1120, 1060, 1000 cm^{-1}; ^1H NMR (CCl_4) δ 0.87 (3 H, t, J = 6), 1.00–1.68 (6 H, m), 1.08 (9 H, s), 2.33 (2 H, t, J = 7). Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 77.04; H, 12.68.

General Procedure for the Condensation of Ketones 1 in THF. Preparation of (4*SR*,5*SR*)-2,2-Dimethyl-4-ethyl-5-hydroxy-5-phenyl-3-pentanone (2b). The following procedure for the preparation of **2b** illustrates the condensations carried out in THF. A solution of lithium diisopropylamide, prepared from 0.16 mL (0.11 g, 1.1 mmol) of diisopropylamine and 0.74 mL (1.1 mmol) of a 1.50 M solution of *n*-butyllithium in hexane, in 5 mL of THF was cooled to −78 °C and 0.16 mL (0.13 g, 1.0 mmol) of 2,2-dimethyl-3-hexanone was added dropwise over a 30-s period. The solution was stirred for 2 h at −78 °C and 0.10 mL (0.10 g, 1.0 mmol) of benzaldehyde was added. After the solution had stirred for 10 min at −78 °C, 5 mL of saturated aqueous NH_4Cl was added to the cold reaction mixture. The mixture was allowed to warm to room temperature and was diluted with ether, and the ether solution was washed with water and dried ($MgSO_4$). Evaporation of the solvent afforded 0.223 g (95%) of the crude aldol, the ^1H NMR spectrum of which indicated that it was 94% pure. Chromatography of the crude material on silica, eluting with 10% ether/hexane, provided 0.119 (52%) of the pure aldol as a pale yellow oil: IR (film) 3450, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (3 H, t, J = 8), 1.00 (9 H, s), 1.33–1.97 (2 H, m), 3.07–3.40 (2 H, m), 4.77 (1 H, d, J = 5), 7.22 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 12.1, 20.0, 26.1, 53.1, 73.4, 126.2, 127.3, 128.1, 142.3, 222.4. An analytical sample was prepared by bulb-to-bulb distillation (110 °C (bath temperature), 0.04 torr). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.89; H, 9.46. Found: C, 76.99; H, 9.37.

(4*SR*,5*SR*)-2,2-Dimethyl-5-hydroxy-5-phenyl-4-propyl-3-pentanone (2c). Aldol condensation of 2,2-dimethyl-3-heptanone with benzaldehyde using the standard conditions gave 0.243 g (98%) of the crude aldol, the ^1H NMR spectrum of which indicated that 88% of the starting ketone had condensed. Chromatography of the crude material on silica, eluting with 10% ether/hexane, gave 0.064 g (26%) of the pure aldol as a pale yellow oil: IR (film) 3480, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, t, J = 7), 0.93–1.77 (4 H, m), 1.05 (9 H, s), 3.20 (2 H, m), 4.78 (1 H, d, J = 4), 7.23 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 14.4, 21.3, 26.2, 28.8, 45.0, 52.1, 73.4, 126.0, 127.3, 128.2, 141.9 (the carbonyl resonance was not detected). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.26; H, 9.81.

(4*SR*,5*SR*)-4-Butyl-2,2-dimethyl-5-hydroxy-5-phenyl-3-pentanone (2d). Aldol condensation of 2,2-dimethyl-3-octanone with benzaldehyde under the standard conditions using a 4.5-h enolization time afforded 0.239 g (91%) of the crude aldol, the ^1H NMR spectrum of which indicated that 98% of the starting ketone had condensed. Bulb-to-bulb distillation of the crude material (140 °C (bath temperature), 0.04 torr) furnished 0.206 g (79%) of the pure aldol as a clear, colorless viscous oil: IR (film) 3480, 1685 cm^{-1}; ^1H NMR (CCl_4) δ 0.79 (3 H, t, J = 7), 0.89–1.82 (6 H, m), 0.98 (9 H, s), 3.16 (2 H, m), 4.66 (1 H, d, J = 5), 7.16 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 13.6, 22.9, 26.2, 26.6, 30.0, 44.9, 52.4, 73.6, 126.0, 127.3, 128.1, 142.2, 220.3; mass spectrum (70 eV), m/e 262 (0.03), 205 (0.07), 156 (1.14), 106 (6.16), 99 (7.32), 77 (6.56), 71 (6.74), 57 (8.70), 43 (10.40). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.63; H, 9.96.

Repetition of this procedure using instead a 1-h enolization time gave 0.220 g (86%) of the crude material, the ^1H NMR spectrum of which showed that it was 28% condensed.

General Procedure for the Condensation of Ketones 1 in Pentane. Preparation of (4*SR*,5*RS*)-2,2-Dimethyl-4-ethyl-5-hydroxy-5-phenyl-3-pentanone (3b). The following procedure for the preparation of **3b** illustrates the condensations carried out in pentane. To a solution of lithium diisopropylamide, prepared from 0.16 mL (0.11 g, 1.1 mmol) of diisopropylamine and 0.74 mL (1.1 mmol) of a 1.50 M solution of *n*-butyllithium in hexane, in 5 mL of pentane at room temperature was added dropwise over a 1-min period 0.16 mL (0.13 g, 1.0 mmol) of 2,2-dimethyl-3-hexanone. The solution was stirred for 2.5 h at room temperature and 0.10 mL (0.10 g, 1.0 mmol) of benzaldehyde was added. After the solution had stirred for 20 min at room temperature, 5 mL of saturated aqueous NH_4Cl was added. The reaction mixture was diluted with ether, and the ether solution was washed with 10% aqueous $NaHSO_3$ and water and then was dried ($MgSO_4$). Evaporation of the solvent afforded 0.184 g (79%) of the crude aldol, the ^1H NMR spectrum of which indicated that 80% of the starting ketone had condensed and that the aldol product was an 85:15 mixture of **3b** and **2b**. Chromatography of the crude material on silica, eluting with 10% ether/hexane, provided 0.079 g (34%) of the pure aldol as a pale yellow oil: IR (film) 3460, 1680 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ 0.80–1.03 (3 H, m), 0.92 (9 H, s), 1.13–1.82 (2 H, m), 3.10 (1 H, q, J = 6), 4.77 (1 H, d, J = 6), 7.20 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 11.8, 23.4, 25.9, 53.4, 74.6, 126.1, 127.4, 128.2, 144.0 (the carbonyl resonance was not observed). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.89; H, 9.46. Found: C, 76.67; H, 9.40.

(4*SR*,5*RS*)-2,2-Dimethyl-5-hydroxy-5-phenyl-4-propyl-3-pentanone (3c). Aldol condensation of 2,2-dimethyl-3-heptanone with benzaldehyde in pentane under the standard conditions gave 0.182 g (73%) of crude aldol, the ^1H NMR spectrum of which indicated that 94% of the starting ketone had condensed and that the aldol product was greater than 95% anti. Chromatography of the crude material on silica, eluting with 10% ether/hexane, gave 0.104 g (42%) of the pure aldol as a pale yellow oil: IR (film) 3460, 1690 cm^{-1}; ^1H NMR (CCl_4 + D_2O) δ 0.73–1.03 (3 H, m), 0.87 (9 H, s), 1.07–1.62 (4 H, m), 3.10 (1 H, m), 4.55 (1 H, d, J = 7), 7.13 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.5, 25.9, 32.5, 44.7, 51.6, 74.7, 126.0, 127.4, 128.2, 143.7, 222.0. Anal. Calcd for $C_{16}H_{24}O_2$:

(26) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(27) F. C. Whitmore, C. I. Noll, and V. C. Meunier, *J. Am. Chem. Soc.*, 61, 685 (1939).

C, 77.38; H, 9.74. Found: C, 77.18; H, 9.70.

(4*SR*,5*RS*)-4-Butyl-2,2-dimethyl-5-hydroxy-5-phenyl-3-pentanone (3d). Aldol condensation of 2,2-dimethyl-3-octanone with benzaldehyde using the standard procedure on a 2.00-mmol scale, a 30-min enolization time, and a 7.5-h condensation time afforded 0.493 g (94%) of the crude aldol, the ^{1}H NMR spectrum of which indicated that 82% of the starting ketone had condensed and that the aldol product was greater than 95% anti. Chromatography of the crude material on silica, eluting with 10% ether/hexane, furnished 0.137 g (26%) of the pure aldol as a pale yellow oil: IR (film) 3450, 1680 cm^{-1}; ^{1}H NMR (CCl_4 + D_2O) δ 0.83 (3 H, t, J = 7), 0.87 (9 H, s), 1.03–1.63 (6 H, m), 3.08 (1 H, q, J = 7), 4.56 (1 H, d, J = 7), 7.12 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.6, 25.7, 29.4, 29.9, 44.6, 51.6, 74.3, 125.8, 127.2, 128.1, 143.5, 221.9. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.98; H, 10.12.

General Procedure for the Preparation of Syn Silyloxy Aldols 5. Preparation of (4*SR*,5*SR*)-2,2-Dimethyl-4-ethyl-5-phenyl-5-(trimethylsilyl)oxy-3-pentanone (5b). The following procedure for the preparation of **5b** illustrates the general method. A solution of lithium diisopropylamide, prepared from 0.16 mL (0.11 g, 1.1 mmol) of diisopropylamine and 0.74 mL (1.1 mmol) of a 1.50 M solution of *n*-butyllithium in hexane, in 5 mL of THF was cooled to −78 °C and 0.16 mL (0.13 g, 1.0 mmol) of 2,2-dimethyl-3-hexanone was added dropwise over a 1-min period. The solution was stirred for 3 h at −78 °C and 0.10 mL (0.10 g, 1.0 mmol) of benzaldehyde was added. After the solution had stirred for 20 min at −78 °C, 0.13 mL (0.11 g, 1.0 mmol) of freshly distilled chlorotrimethylsilane was added and the mixture was allowed to warm to room temperature. After the mixture had stirred for 1.5 h at room temperature it was poured into 25 mL of pentane and 25 mL of saturated aqueous $NaHCO_3$, the layers were separated, and the organic phase was dried (Na_2SO_4). Evaporation of the solvent provided 0.262 g (85%) of the crude silyloxy ketone. Bulb-to-bulb distillation (115 °C (bath temperature), 0.04 torr) afforded 0.194 g (63%) of the pure material as a clear colorless oil: IR (film) 1690, 1250, 900 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.07 (9 H, s), 0.79 (9 H, s), 0.98 (3 H, t, J = 8), 1.82 (2 H, m), 3.20 (1 H, dt, J = 9, 5), 4.78 (1 H, d, J = 9), 7.22 (5 H, s). Anal. Calcd for $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.87. Found: C, 70.22; H, 9.72.

(4*SR*,5*SR*)-2,2-Dimethyl-5-phenyl-4-propyl-5-(trimethylsilyl)oxy-3-pentanone (5c). Condensation of 2,2-dimethyl-3-heptanone with benzaldehyde using the general procedure gave 0.274 g (85%) of the crude silyloxy ketone. Bulb-to-bulb distillation (125 °C (bath temperature), 0.04 torr) of the crude material furnished 0.231 g (72%) of the pure material as a clear colorless oil: IR (film) 1690, 1250, 880 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.07 (9 H, s), 0.78 (9 H, s), 0.97 (3 H, t, J = 7), 1.13–1.90 (4 H, m), 3.20 (1 H, dt, J = 9, 5), 4.75 (1 H, d, J = 9), 7.20 (5 H, s). Anal. Calcd for $C_{19}H_{32}O_2Si$: C, 71.19; H, 10.06. Found: C, 71.09; H, 10.06.

(4*SR*,5*SR*)-4-Butyl-2,2-dimethyl-5-phenyl-5-(trimethylsilyl)oxy-3-pentanone (5d). Condensation of 2,2-dimethyl-3-octanone with benzaldehyde by the general procedure using a 4-h enolization time and a 15-min condensation time gave 0.319 g (95%) of the crude silyloxy ketone. Bulb-to-bulb distillation (125 °C (bath temperature), 0.04 torr) afforded 0.249 g (75%) of the pure material as a clear colorless oil: IR (film) 1690, 1250, 890 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.05 (9 H, s), 0.77 (9 H, s), 0.98 (3 H, t, J = 6), 1.17–1.58 (4 H, m), 1.58–1.90 (2 H, m), 3.20 (1 H, dt, J = 9, 5), 4.77 (1 H, d, J = 9), 7.20 (5 H, s). An analytical sample was obtained by preparative GLC (10% SE-30, 10 ft × 0.25 in., 200 °C). Anal. Calcd for $C_{20}H_{34}O_2Si$: C, 71.80; H, 10.24. Found: C, 71.86; H, 10.08.

(4*SR*,5*SR*)-2,2-Dimethyl-4-ethyl-5-phenyl-5-(trimethylsilyl)oxy-3-pentanone (6b). A mixture of 0.0564 g (0.241 mmol) of a 5:1 mixture of aldols **3b** and **2b** and 0.15 mL (0.12 g, 0.59 mmol) of bis(trimethylsilyl)acetamide was heated at 95°C for 20 h. The reaction mixture was then cooled and diluted with hexane, and the hexane solution was washed with water and dried ($MgSO_4$). Evaporation of the solvent afforded 0.0669 g (91%) of a 5:1 mixture of the anti and syn silyloxy ketones as a yellow oil: IR (film) 1700, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) anti δ 0.15 (9 H, s), 0.70 (3 H, t, J = 8), 0.93–1.47 (2 H, m), 1.33 (9 H, s), 3.30 (1 H, m), 4.68 (1 H, d, J = 9), 7.32 (5 H, s). An analytical sample was obtained by preparative GLC (10% SE-30, 10 ft × 0.25 in., 200 °C). Anal. Calcd for $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.87. Found: C, 70.48; H, 9.80.

(4*SR*,5*RS*)-2,2-Dimethyl-5-phenyl-4-propyl-5-(trimethylsilyl)oxy-3-pentanone (6c). To a solution of 0.0721 g (0.290 mmol) of anti aldol **3c** in 2 mL of CH_2Cl_2 at 0 °C was added 0.10 mL (0.10 g, 0.68 mmol) of *N*-(trimethylsilyl)imidazole. After the mixture had stirred for 3 h at 0 °C, the solvent was removed by evaporation and the residue was passed through a short pad of silica, eluting with 20% ether/hexane. Evaporation of the solvent afforded 0.0952 g (100%) of the anti silyloxy ketone as a clear colorless oil: IR (film) 1700, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ −0.15 (9 H, s), 0.64 (3 H, t, J = 7) 0.77–1.42 (4 H, m) 1.19 (9 H, s), 3.32 (1 H, m), 4.46 (1 H, d, J = 10), 7.31 (5 H, s). An analytical sample was obtained by preparative GLC (10% SE-30, 10 ft × 0.25 in., 200 °C). Anal. Calcd for $C_{19}H_{32}O_2Si$: C, 71.19; H, 10.06. Found: C, 71.11; H, 9.88.

(4*SR*,5*RS*)-4-Butyl-2,2-dimethyl-5-phenyl-5-(trimethylsilyl)oxy-3-pentanone (6d). A mixture of 0.255 g (0.973 mmol) of anti aldol **3d** and 0.50 mL (0.41 g, 2.0 mmol) of bis(trimethylsilyl)acetamide was heated at 90 °C for 48 h. The reaction mixture was then cooled and diluted with hexane, and the hexane solution was washed with water and dried ($MgSO_4$). Evaporation of the solvent afforded 0.246 g (75%) of the anti silyloxy ketone as a yellow oil: IR (film) 1700, 1250 cm^{-1}; ^{1}H NMR (CCl_4) δ −0.05 (9 H, s), 0.77 (3 H, t, J = 6), 0.90–1.50 (6 H, m), 1.27 (9 H, s), 3.20 (1 H, m), 4.62 (1 H, d, J = 10), 7.28 (5 H, s). An analytical sample was obtained by preparative GLC (10% SE-30, 10 ft × 0.25 in., 200 °C). Anal. Calcd for $C_{20}H_{34}O_2Si$: C, 71.80; H, 10.24. Found: C, 72.08; H, 10.08.

Enolization in Pentane Followed by Condensation in THF. Preparation of 2d. To a solution of lithium diisopropylamide, prepared from 0.16 mL (0.11 g, 1.1 mmol) of diisopropylamine and 0.74 mL (1.1 mmol) of a 1.50 M solution of *n*-butyllithium in hexane, in 10 mL of pentane at room temperature was added dropwise over a 1-min period 0.19 mL (0.15 g, 1.0 mmol) of 2,2-dimethyl-3-octanone. The solution was stirred for 4 h at room temperature and the solvent was removed by evaporation, leaving a pale oil which crystallized to white needles. The residue was dissolved in 5 mL of THF, the solution was cooled to −78 °C, and 0.10 mL (0.10 g, 1.0 mmol) of benzaldehyde was added. After the solution had stirred for 15 min at −78 °C, 5 mL of saturated aqueous NH_4Cl was added and the mixture was allowed to warm up to room temperature. The reaction mixture was diluted with ether, and the ether solution was washed with water and dried ($MgSO_4$). Evaporation of the solvent left 0.258 g (98%) of the aldol product as a pale yellow oil. The ^{1}H NMR spectrum of this material indicated that 65% of the starting ketone had condensed and that the aldol product was greater than 98% syn.

Enolization in THF Followed by Condensation in Pentane. Preparation of 3d. A solution of lithium diisopropylamide, prepared from 0.13 mL (0.093 g, 0.92 mmol) of diisopropylamine and 0.63 mL (0.84 mmol) of a 1.34 M solution of *n*-butyllithium in hexane, in 3 mL of THF was cooled to −78 °C and 0.125 g (0.800 mmol) of 2,2-dimethyl-3-octanone was added dropwise over a 1-min period. The solution was stirred for 1.5 h at −78 °C and then allowed to warm to room temperature, and the solvent was removed by evaporation, leaving a yellow viscous liquid. The residue was dissolved in 5 mL of pentane, and 0.082 mL (0.085 g, 0.80 mmol) of benzaldehyde was added. After the solution had stirred for 6 h at room temperature, 5 mL of saturated aqueous NH_4Cl was added. The reaction mixture was diluted with ether, and the ether solution was washed with water and dried ($MgSO_4$). Evaporation of the solvent left 0.122 g (58%) of the aldol as a pale yellow oil. The ^{1}H NMR spectrum of this material indicated that 75% of the starting ketone had condensed and that the aldol product was greater than 98% anti.

Low-Temperature Condensations in Pentane. Preparation of 2d and 3d. Aldol condensation of 2,2-dimethyl-3-octanone with benzaldehyde in 10 mL of pentane was carried out by using the general procedure, with the following changes. The enolate was allowed to form over 3 h, after which the solution was cooled to −78 °C and 0.10 mL (0.10 g, 1.0 mmol) of benzaldehyde was added. After the reaction mixture had stirred for 15 min at −78 °C, 5 mL of saturated aqueous NH_4Cl was added and the mixture was allowed to warm to room temperature. The standard workup

procedure afforded 0.239 g (91%) of the aldol product as a pale yellow oil. The ^1H NMR spectrum of this material indicated that 70% of the starting ketone had condensed and that the aldol product was a 90:10 syn:anti mixture.

The above procedure was repeated, with the exception that the condensation mixture was allowed to warm to room temperature and was stirred at room temperature for 30 min before it was quenched. The reaction mixture was then quenched and worked up as before to yield 0.255 g (97%) of the aldol product as a pale yellow oil. The ^1H NMR spectrum of this material indicated that 80% of the starting ketone had condensed, and that the aldol product was greater than 98% anti.

(4*SR*,5*SR*)- and (4*SR*,5*RS*)-5-Hydroxy-5-phenyl-2,2,4-trimethyl-3-pentanone (2a and 3a). Aldol condensation of 2,2-dimethyl-3-pentanone with benzaldehyde in 10 mL of pentane using the general procedure, a 3-h enolization time, and a 15-min condensation time afforded 0.194 g (92%) of the known aldol products as a pale yellow oil. The ^1H NMR spectrum of this material was consistent with spectra published elsewhere,[4] and indicated that 80% of the starting ketone had condensed and that the aldol product was an 80:20 syn:anti mixture. From this value, assuming that the syn:anti ratio at time 0 was 100:0, the half-life for equilibration at 25 °C may be estimated to be 45 min.

(4*SR*,5*SR*)-5-Hydroxy-5-phenyl-2,2,4-trimethyl-3-pentanone (2a). Aldol condensation of 2,2-dimethyl-3-pentanone with benzaldehyde in 10 mL of pentane was carried out by using the general procedure, with the following changes. The enolate was allowed to form over a 2-h period, after which the solution was cooled to −78 °C and 0.10 mL (0.10 g, 1.0 mmol) of benzaldehyde was added. After the reaction mixture had stirred for 20 min at −78 °C, 5 mL of saturated aqueous NH_4Cl was added and the mixture was allowed to warm to room temperature. The standard workup procedure afforded 0.166 g (79%) of the aldol product as a clear colorless oil. The ^1H NMR spectrum of this material indicated that 75% of the starting ketone had condensed and that the aldol product was greater than 98% syn.

2-Pentadecyl-1,3-dithiane (11). To a solution of 3.61 g (15.0 mmol) of hexadecanal in 40 mL of $CHCl_3$ at −20 °C was added 1.51 mL (1.63 g, 15.0 mmol) of 1,3-propanedithiol. The solution was allowed to warm to room temperature and was stirred for 1 h, after which it was cooled to −20 °C and 0.18 mL (0.21 g, 1.5 mmol) of boron trifluoride etherate was added. The reaction mixture was allowed to warm to room temperature and was stirred for 3.5 h. The mixture was then washed with water, 10% aqueous KOH, water, and brine and was dried ($MgSO_4$). Evaporation of the solvent gave 4.28 g of the crude dithiane as a yellow solid. Recrystallization from ethanol provided 2.50 g (50%) of the pure dithiane as a white waxy solid, mp 37–37.5 °C. Concentration of the mother liquors provided an additional 0.88 g (18%) of the product: IR (CCl_4) 1460, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3 H, m), 1.25 (26 H, br s), 1.67 (2 H, m), 2.00 (2 H, m), 2.77 (4 H, m), 3.93 (1 H, t, J = 7). Preparative TLC on silica, eluting with 20% ether/hexane, gave the analytical sample, mp 41.5–43 °C. Anal. Calcd for $C_{19}H_{38}S_2$: C, 69.02; H, 11.58. Found: C, 68.89; H, 11.48.

2-(1-Hydroxy-1-methylethyl)-2-pentadecyl-1,3-dithiane (12). To a solution of 2.40 g (7.25 mmol) of dithiane **11** in 40 mL of THF at −20 °C was added 5.3 mL (8.0 mmol) of a 1.50 M solution of *n*-butyllithium in hexane. The mixture was stirred for 2.25 h at −20 °C after which it was cooled to −78 °C and 0.54 mL (0.42 g, 7.3 mmol) of acetone was added at such a rate as to keep the temperature of the mixture below −65 °C. After the mixture had stirred for 1 h at −65 °C it was warmed to 0 °C and was allowed to stand at 0 °C overnight. The solution was then poured into 75 mL of water and extracted with CH_2Cl_2. The organic extracts were washed with water and brine and were dried ($MgSO_4$). Evaporation of the solvent left 4.36 g of the crude addition product. Chromatography of the crude material on silica, eluting with 20% ether/hexane, provided 1.98 g (70%) of the pure product as a clear colorless oil: IR (film) 3480, 1460, 950, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3 H, m), 1.28 (26 H, s), 1.42 (6 H, s), 1.50–2.12 (4 H, m), 2.48 (1 H, s), 2.87 (4 H, m). Anal. Calcd for $C_{22}H_{44}OS_2$: C, 67.98; H, 11.41. Found: C, 68.29; H, 11.38.

2-Hydroxy-2-methyl-3-octadecanone (13). A suspension of 1.92 g (4.93 mmol) of thioketal **12** in 100 mL of 4:1 v/v acetonitrile–water was added to a rapidly stirring suspension of 3.00 g (11.0 mmol) of $HgCl_2$ and 0.54 g (5.4 mmol) of $CaCO_3$ in 50 mL of 4:1 v/v acetonitrile–water under nitrogen. The mixture was heated at reflux for 19 h, during which time a thick white precipitate formed. The reaction mixture was cooled and filtered through a pad of Celite, and the filter pad was washed well with 1:1 hexane–CH_2Cl_2. The organic phase was washed with 5 M NH_4OAc, water, and brine and then dried ($MgSO_4$). Evaporation of the solvent afforded 1.30 g (89%) of the ketone as a pale yellow oil: IR (film) 3470, 1710, 1460, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, m), 1.30 (26 H, s), 1.37 (6 H, s), 2.53 (2 H, t, J = 7), 3.80 (1 H, br s). Anal. Calcd for $C_{19}H_{38}O_2$: C, 76.45; H, 12.83. Found: C, 76.47; H, 12.76.

2-Methyl-2-(trimethylsilyl)oxy-3-octadecanone (14). A mixture of 0.973 g (3.26 mmol) of hydroxy ketone **13** and 0.64 mL (0.53 g, 2.6 mmol) of bis(trimethylsilyl)acetamide was stirred under nitrogen at 50 °C for 19 h. An additional 0.32 mL (0.26 g, 1.3 mmol) of bis(trimethylsilyl)acetamide was then added, and the mixture was stirred at 90 °C for 24 h. The mixture was diluted with hexane, and the hexane solution was washed with water and dried ($MgSO_4$). Evaporation of the solvent left 1.20 g (99%) of the crude product, which was chromatographed on silica, eluting with 5% ether/hexane, to give 1.05 g (87%) of the silyloxy ketone as a clear colorless liquid: IR (film) 1720, 1250, 1040, 840 cm^{-1}; ^1H NMR (CCl_4) δ 0.30 (9 H, s), 1.00 (3 H, m), 1.40 (26 H, s), 1.43 (6 H, s), 2.60 (2 H, t, J = 7). An analytical sample was prepared by preparative GLC (10% SE-30, 10 ft × 0.25 in., 210 °C). Anal. Calcd for $C_{22}H_{46}O_2Si$: C, 71.28; H, 12.51. Found: C, 71.50; H, 12.36.

(4*SR*,5*RS*)- and (4*RS*,5*RS*)-5-Hydroxy-2-methyl-4-tetradecyl-2-(trimethylsilyl)oxy-3-eicosanone (15 and 16). A solution of lithium diisopropylamide, prepared from 0.16 mL (0.11 g, 1.1 mmol) of diisopropylamine and 0.76 mL (1.1 mmol) of a 1.39 M solution of *n*-butyllithium in hexane, in 1.5 mL of THF was cooled to −78 °C and 0.364 g (0.982 mmol) of ketone **14** was added. The solution was stirred for 9 h at −78 °C and a solution of 0.249 g (1.04 mmol) of hexadecanal in 1.5 mL of THF was added. After the solution had stirred for 5 min at −78 °C, 5 mL of saturated aqueous $NaHCO_3$ was added and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with ether, and the ether solution was washed with water and brine and was dried ($MgSO_4$). Evaporation of the solvent left 0.594 g (99%) of the crude aldol, the ^1H NMR spectrum of which indicated that 60% of the starting ketone had condensed. This material proved to be sensitive to chromatography and was generally used in its crude form. However, a pure sample could be obtained by preparative TLC on silica, eluting with 5% ether/hexane: IR (film) 3500, 1700, 1460, 1250, 840 cm^{-1}; ^1H NMR (CCl_4) δ 0.32 (9 H, s), 0.98 (6 H, m), 1.37 (60 H, br s), 2.40 (1 H, m), 3.37 (1 H, m), 3.62 (1 H, m). Anal. Calcd for $C_{38}H_{78}O_3Si$: C, 74.69; H, 12.87. Found: C, 75.02; H, 12.65.

Methyl Isocorynomycolate (9). A solution of 0.594 g 0.972 mmol) of crude, 60% condensed aldols **15** and **16**, prepared as described above, in 5 mL of THF was added to a solution of 0.905 g (3.97 mmol) of H_5IO_6 in 10 mL of THF, and the mixture was stirred for 5 h at room temperature. The reaction mixture was then diluted with ether, and the ether solution was washed with brine and dried ($MgSO_4$). Evaporation of the solvent left 0.634 g of a white solid, which was dissolved in 10 mL of 1:1 acetone–ether and treated with excess ethereal diazomethane at 0 °C. The reaction mixture was diluted with ether, and the ether solution was washed with brine and dried ($MgSO_4$). Evaporation of the solvent left 0.493 g (99%) of a white solid which was chromatographed on silica, eluting with 8% ether/hexane, to give 0.224 g (45%) of a fraction consisting predominantly of methyl hexadecanoate, 0.176 g (36%) methyl isocorynomycolate (**9**), mp 70–71 °C (lit.[28] mp 68–70 °C), and 0.0399 g (7.8%) of methyl corynomycolate (**10**), mp 56–58 °C (lit.[28] mp 57–58 °C).

Acknowledgment. This work was supported by a grant from the United States Public Health Service (AI-15027).

(28) (a) J. Polonsky and E. Lederer, *Bull. Soc. Chim. Fr.*, 504 (1954); (b) E. Lederer, V. Portelance, and K. Serck-Hanssen, *ibid.*, 413 (1952).

We thank Dr. W. A. Kleschick for preparing compounds **5a** and **6a**.

Registry No. **1a**, 564-04-5; **1b**, 5405-79-8; **1c**, 19078-97-8; **1d**, 5340-64-7; (±)-**2a**, 87280-57-7; (±)-**2b**, 87280-40-8; (±)-**2c**, 87280-41-9; (±)-**2d**, 87280-42-0; (±)-**3b**, 87280-43-1; (±)-**3c**, 87280-44-2; (±)-**3d**, 87280-45-3; (±)-**5b**, 87280-46-4; (±)-**5c**, 87280-47-5; (±)-**5d**, 87280-48-6; (±)-**6b**, 87280-49-7; (±)-**6c**, 87280-50-0; (±)-**6d**, 87280-51-1; (±)-**9**, 87333-63-9; **11**, 59014-51-6; **12**, 87280-52-2; **13**, 87280-53-3; **14**, 87280-54-4; (±)-**15**, 87280-55-5; (±)-**16**, 87280-56-6; 2,2-dimethyl-3-hexanol, 4209-90-9; 2,2-dimethyl-3-heptanol, 19549-70-3; 2,2-dimethyl-3-octanol, 19841-72-6.

Stereochemistry of Horse Liver Alcohol Dehydrogenase Mediated Oxidoreduction of 2-Brendanone Type Cage-Shaped Tricyclic Ketones and the Related Stereoisomeric Alcohols[1]

Masao Nakazaki,* Hiroaki Chikamatsu, Takeo Fujii, Yasuyuki Sasaki, and Shizuo Ao

Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560, Japan

Received March 15, 1983

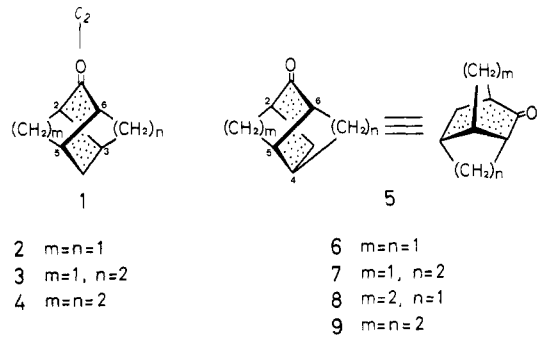
For elucidation of the origin of the inertness exhibited by 2-*twist*-brendanone type ketones **1** toward microbial and HLADH-catalyzed reductions, the stereochemistry of the oxidoreduction of 2-brendanone type ketones **5** and the related alcohols **14** was studied by preparative-scale incubation experiments. Oxidoreduction of 2-brendanone type substrates **5** and **14** by the HLADH–NAD^+ system was found to proceed with much higher rates than those of the 2-*twist*-brendanone type substrates **1** and **10**. The steric courses found in these enzymatic processes were compared with those of microbial processes.

Our continuing interests in the stereochemistry of high-symmetry chiral compounds[2] have prompted us to study the steric course of microbial reduction of C_2 ketones[3] possessing a variety of molecular frameworks, and our efforts in this direction have led us to propose a microbial "*P*-C_2 ketone rule", which summarizes the stereoselectivity exhibited by *Curvularia lunata* and *Rhodotorula rubra* toward these C_2 ketones.[4]

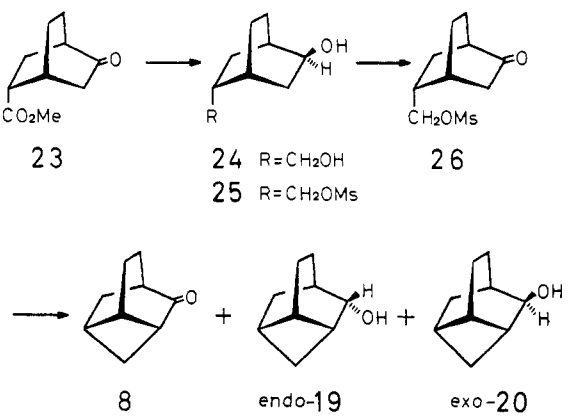
Making a striking contrast with these microbial systems, crystalline horse liver alcohol dehydrogenase (HLADH)[5] was found to exhibit a completely opposite stereoselectivity toward the same class of C_2 ketones, and we showed that another C_2 ketone rule, "*M*-C_2 ketone rule", is to be invoked for predicting the steric course in this biological system.[6]

Further extension of these studies to cage-shaped C_1 ketones[3] of various molecular frameworks has enabled us to formulate a "quadrant rule",[7,8] which summarizes the stereochemistry of these biological oxidoreductions for this type of cage-shaped ketones.[9]

Chart I



Scheme I



What perplexed us during these studies was a peculiar inertness of 2-*twist*-brendanone (**3**)[10] and 2-twistanone (**4**)[10] toward these biological oxidoreductions; we were also puzzled by our finding that the oxidoreductions of D_{2d}

(1) Presented at the 43th Annual Meeting of the Chemical Society of Japan, Tokyo, April 1981: Abstract, Vol. II, p 687.

(2) For a review of the synthesis and stereochemistry of gyrochiral cage-shaped compounds, see: Nakazaki, M.; Naemura, K. *Yuki Gosei Kagaku Kyokaishi* **1982**, *40*, 1128–1144.

(3) In this paper, we conveniently classify ketones according to their symmetry around the carbonyl center: C_1 ketones belong to the C_1 point group and have no symmetry element passing through the carbonyl center, and C_2 ketones belong to the C_2 point group and have a C_2 symmetry axis coincident with the carbonyl axis.

(4) For references concerning the microbial "*P*-C_2 ketone rule" see: Nakazaki, M.; Chikamatsu, H.; Nishino, M.; Murakami, H. *J. Org. Chem.* **1981**, *46*, 1151–1156.

(5) Abbreviations used: HLADH, horse liver alcohol dehydrogenase; NADH and NAH^+, reduced and oxidized forms, respectively, of nicotinamide adenine dinucleotide; FMN, flavin mononucleotide.

(6) For references concerning the HLADH "*M*-C_2 ketone rule" see: (a) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Suzuki, T.; Iwasaki, M.; Sasaki, Y.; Fujii, T. *J. Org. Chem.* **1981**, *46*, 2726–2730. (b) Nakazaki, M.; Naemura, K.; Chikamatsu, H.; Iwasaki, M.; Hashimoto, M. *Ibid.* **1981**, *46*, 2300–2306.

(7) For references concerning the microbial "quadrant rule" see: Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Asao, M. *J. Org. Chem.* **1980**, *45*, 4432–4440 and also see ref 8.

(8) The HLADH "quadrant rule": Nakazaki, M.; Chikamatsu, H.; Sasaki, Y. *J. Org. Chem.* **1983**, *48*, 2506–2511.

(9) For a review summarizing our recent studies in this field, see: Nakazaki, M. *Gendai Kagaku* **1982**, 38–47.

(10) For the cage-shaped substrates discussed in this paper, we have used their trivial names. Their IUPAC names are shown in parentheses: D_{2d} 2-dinoradamantanone (tricyclo[3.3.0.0^{3,7}]octan-2-one, 2-*twist*-brendanone (tricyclo[4.3.0.0^{3,8}]nonan-2-one), 2-brendanone (tricyclo[4.2.1.0^{3,7}]nonan-2-one), 2-norbrendanone (tricyclo[3.2.1.0^{3,6}]octan-2-one), 2-isobrendanone (tricyclo[3.3.1.0^{3,6}]nonan-2-one), 2-twistanone (tricyclo[4.4.0.0^{3,8}]decan-2-one), 2-isotwistanone (tricyclo[4.3.1.0^{3,7}]decan-2-one).

0022-3263/83/1948-4337$01.50/0