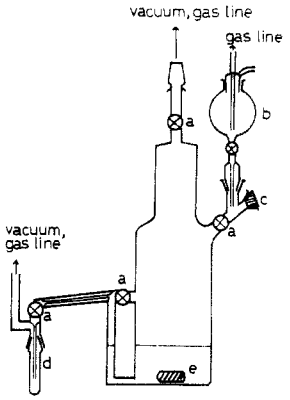

Figure 3. Reactor equipment: a, greaseless valve made of Teflon; b, solvent reservoir; c, silicon rubber stopper; d, sampling vessel; e, spinner.

distilled, and stored in a sealed, glass tube.

The reaction was carried out in a glass reactor equipped with greaseless valves. After the complex of catalyst precursor (0.1 mmol) was dissolved in 1% aqueous diglyme (50 mL) under a nitrogen atmosphere, nitrogen was replaced with hydrogen, the solution being aged for 5 min strictly (essential for reproducibility) under atmospheric pressure of hydrogen, to yield the active hydrido complex. *The PEt_3 complex in its solid form should never be exposed to dry hydrogen. It occasionally reacted explosively.* The epoxide (10 mmol) was injected with a syringe through a silicon rubber stopper to start the reaction. The reaction was followed by gas chromatographic analysis [column: polyethylene glycol (20 M), 2 m] of a small portion of the reaction mixture (ca. 0.2 mL) which was sampled by use of the equipment (Figure 3) at appropriate intervals without any contact of the reaction system with air.

After the hydrogenation reaction, oligomers were separated from the reaction mixture by the evaporation of solvent and other products under vacuum ($<1 \times 10^{-4}$ torr) at 30 °C. Oligomers were separated by TLC and by the Kugelrohr method. TLC analyses showed that oligomers consisted of more than ten species. The average molecular weights of oligomers were measured by means of a vapor-pressure osmometer (Hitachi 115). 2,5-Diphenyl-1,4-dioxane was separated in crystalline form by use of the Kugelrohor method with ca. 20% of oligomers when the PEt_3 complex was used: mass spectru, m/e (M^+) 240; mp 170 °C; ^1H NMR ($CDCl_3$) δ 3.63 (q, 2 H), 4.08 (q, 2 H), 4.70 (q, 2 H), 7.35 (m, 10 H), $J_{\alpha-\beta}$ = 12 Hz, $J_{\beta-\gamma}$ = 10 Hz, $J_{\alpha-\gamma}$ = 3 Hz.

Registry No. Styrene oxide, 96-09-3; β-phenylethyl alcohol, 60-12-8; phenylacetaldehyde, 122-78-1; $[Rh(NBD)(PEt_3)_2]^+ClO_4^-$, 65466-19-5; $[Rh(NBD)(PMe_3)_3]^+ClO_4^-$, 76963-03-6; $[Rh(NBD)(PPh_3)_2]^+ClO_4^-$, 32799-31-8; $[Rh(NBD)(diphos)]^+ClO_4^-$, 32799-34-1; $[Rh(NBD)(PEt_3)_2]^+BPh_4^-$, 76986-43-1; $[Rh(NBD)(PPh_3)_2]^+BPh_4^-$, 31666-38-3.

Acyclic Stereoselection. 12. Double Stereodifferentiation with Mutual Kinetic Resolution. A Superior Class of Reagents for Control of Cram's Rule Stereoselection in Synthesis of *erythro*-α-Alkyl-β-hydroxy Carboxylic Acids from Chiral Aldehydes[1,2]

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Chiral α-[(trimethylsilyl)oxy] ketones **7-9** have been prepared and their aldol condensations studied. Compound **8** shows from good to excellent inherent diastereoface selectivity in reactions with achiral aldehydes. Stereoselectivity is related to the size of the alkyl group attached to the aldehyde carbonyl; highest selectivity is observed with diphenylacetaldehyde (>10:1) and pivaldehyde (>19:1). Ketone **8** also shows high diastereoface selectivity in its reactions with chiral, racemic aldehydes **21**, **25**, **29**, and **17**, only one stereoisomeric aldol being obtained in each case. Furthermore, the four aforementioned aldehydes show much higher diastereoface selectivity with ketone **8** than they do with the related ketone **1**. As a result, the reactions of racemic **8** with these chiral, racemic aldehydes show a high degree of "mutual kinetic resolution". In fact, the rate of the (*R*)-enolate plus (*R*)-aldehyde condensation is at least 35 times the rate of the (*R*)-enolate plus (*S*)-aldehyde condensation. It is shown by simple logical argument that such mutual kinetic resolution is expected in reactions between two chiral racemic compounds and that the magnitude of the effect should be proportional to the inherent diastereoselectivity shown by each compound in its reaction with achiral reaction partners. Thus, reagents such as **8** can be used to obtain the benefits of double stereodifferentiation even in the racemic form. As an application of the chemistry developed, (±)-blastmycinone (**47**) has been prepared in four steps from ketone **9** (20% overall yield).

In previous papers in this series, we have introduced ketone **1** as a reagent for the achieving high erythro selectivity[3] in preparation of α-alkyl-β-hydroxy carboxylic acids,[4] aldehydes,[5] and ketones.[6] Although this compound

(1) For part 11 see C. H. Heathcock, C. T. White, J. J. Morrison, and D. VanDerveer, *J. Org. Chem.*, **46**, 1296 (1981).

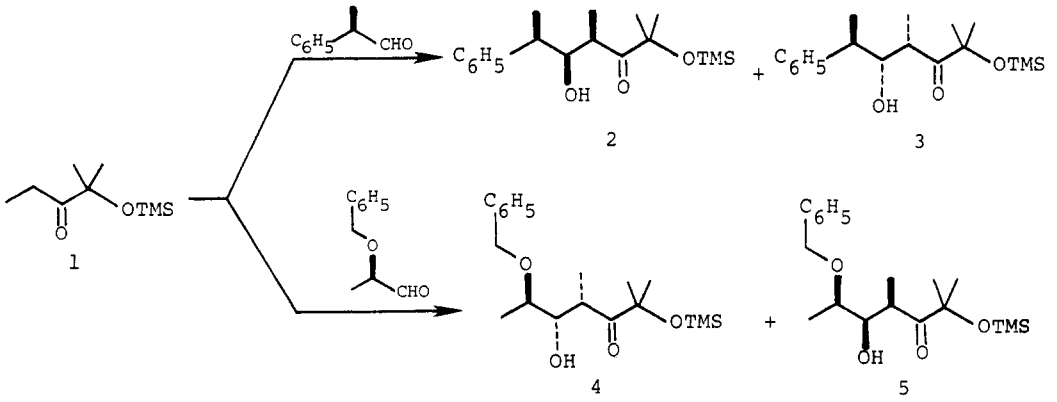
(2) A portion of this work has been communicated in preliminary form: (a) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, and J. E. Sohn, 2nd International IUPAC Symposium on Organic Synthesis, Jerusalem, Sept 12, 1978. (b) C. H. Heathcock, M. C. Pirrung, C. T. Buse, J. P. Hagen, S. D. Young, and J. E. Sohn, *J. Am. Chem. Soc.*, **101**, 7077 (1979).

(3) It is convenient to have stereochemical nomenclature which is invariant of the nature of the α-alkyl group. We prefer the prefixes erythro and threo and use them in the following sense: when the backbone of the aldol is written in an extended (zig-zag) manner, if the α-alkyl substituent and the β-hydroxy substituent both extend toward the viewer or away from the viewer, this is the erythro diastereomer.

(4) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).

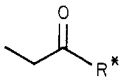
0022-3263/81/1946-2290$01.25/0

Scheme I



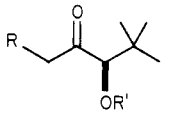
shows good simple diastereoselection,[1] it does not solve the problem of diastereoface selectivity in addition to chiral aldehydes. For example, the enolate of **1** reacts with α-phenylpropionaldehyde to give β-hydroxy ketones **2** and **3** (Scheme I) in a ratio of 4:1[4] and with *O*-benzyllactaldehyde to give β-hydroxy ketones **4** and **5** in a ratio of 2:1.[5]

One possible solution to this problem is double stereodifferentiation. Thus, by employing a second chiral element in addition to a chiral aldehyde, the effective diastereoface selectivity of the aldehyde may be altered.[1] In order for this strategy to be employed for the synthesis of β-hydroxy acids and aldehydes, we need a readily available ethyl ketone (**6**) which possesses several prop-



6

erties. First, the group R* must be large, so that the resulting enolate will show high erythro selectivity. Second, R* must be easily convertible into OH or H. Third, R* must be chiral, and the resulting enolate must show substantial diastereoface selectivity in its reactions with achiral aldehydes, since the greater the inherent diastereoface selectivity, the more effective **6** will be in enhancing the stereoselectivity of additions to chiral aldehydes. Finally, both enantiomers of **6** should be available. In this paper, we report the synthesis of a compound (ketone **8**),



7, R = H; R′ = $Si(CH_3)_3$
8, R = CH_3; R′ = $Si(CH_3)_3$
9, R = n-C_4H_9; R′ = $Si(CH_3)_3$
10, R = R′ = H
11, R = CH_3; R′ = H
12, R = n-C_4H_9; R′ = H

which meets our first three criteria. Furthermore, we report a suprising discovery—that ketone **8** shows a high degree of mutual kinetic resolution in its reactions with racemic chiral aldehydes and that it shows greatly enhanced "Cram's rule selectivity" even in double racemic reactions. We have also extended our studies to the analogous ketones **7** and **9**.

(5) C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, and D. VanDerveer, *J. Org. Chem.*, **45**, 3846, (1980).
(6) C. T. White and C. H. Heathcock, *J. Org. Chem.*, **46**, 191 (1981).

Table I. Condensation of Ketone 8 with Various Aldehydes

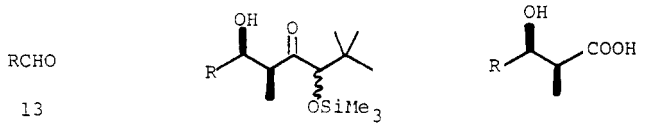
aldehyde	yield of 14, %[a]	diastereomer ratio	yield of 15,[b] %
13a	69	≥9:1	84
13b	75	87:13	62
13c	93	3:1	45
13d	47	≥95:5	57
13e	75	3:1	63

[a] This is the yield of HPLC-purified aldols. For **14b,c,e** the yield refers to the mixture of diastereomers. [b] The diastereomeric purity of **15** was >98% in each case.

Compound **7** is prepared by addition of 1-lithio-1-ethoxyethylene[7] to pivaldehyde. After hydrolysis, hydroxy ketone **10** is produced. Silylation is accomplished by heating with bis(trimethylsilyl)acetamide (BSA) to obtain **7** (31% overall yield). Ketone **8** may be prepared by either of two routes. Addition of 1-lithio-1-methoxypropene[7] to pivaldehyde followed by hydrolysis gives hydroxy ketone **11**. Compound **11** is converted into ketone **8** by being heated with BSA; the overall yield of **8** is 40%. Alternatively, 5-methylhex-4-en-3-one[8] is allowed to react with lithium dimethylcopper, and the resulting enolate mixture is quenched with trimethylsilyl chloride to obtain a silyl enol ether. The crude ether is oxidized by using *m*-chloroperoxybenzoic acid,[9] and the resulting oxidation product is distilled to obtain trimethylsilyloxy ketone **8**. The overall yield of **8** by this simplified procedure is also about 40%. Ketone **12** is prepared by addition of 2-lithio-2-*n*-pentyl-1,3-dithiane to pivaldehyde, followed by hydrolysis. Silylation of **12** provides **9** in 48% overall yield.

Condensations of **8** were carried out with achiral aldehydes **13a–e**. Compound **8** differs from compound **1** in two important respects. First, deprotonation is markedly slower for **8**. Compound **1** is deprotonated by lithium diisopropylamide (LDA) in THF virtually instantaneously at −78 °C. However, with **8** we employ a standard deprotonation time of 2 h. Second, the enolate of **8** seems to be less reactive than that of **1**. In most cases, we add 1.5–2.0 equiv of tetramethylethylenediamine (TMEDA) to the cold enolate solution before addition of the aldehyde. Furthermore, we normally employ longer reaction times with **8** (20–35 min) than with **1** (5–10 min). The aldols produced from **8** and aldehydes **13a–e** (β-hydroxy ketones

(7) J. E. Baldwin, G. A. Höfle, and O. W. Lever, Jr., *J. Am. Chem. Soc.*, **96**, 7125 (1974). Although these authors report only the metalation of methyl vinyl ether, we have found that the more readily available ethyl vinyl ether may be used if the reaction is carried out at 20 °C rather than 0 °C.
(8) G. R. Malone and A. I. Meyers, *J. Org. Chem.*, **39**, 623 (1974).
(9) G. M. Rubottom, M. A. Vasquez, and D. R. Pelagrince, *Tetrahedron Lett.*, 4319 (1974).

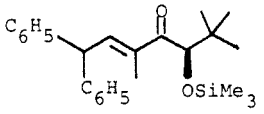


13 14 15

a: R = $(C_6H_5)_2CH$
b: R = $C_6H_5CH_2$
c: R = $(CH_3)_2CH$
d: R = $(CH_3)_3C$
e: R = C_6H_5

14a–e) were each analyzed by ^{13}C NMR spectroscopy and oxidized by periodic acid in aqueous methanol to obtain β-hydroxy acids **15a–e**. Results of this study are summarized in Table I.

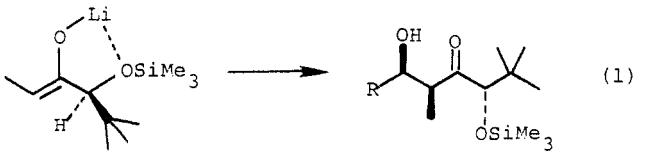
Condensation of **8** with benzaldehyde and isobutyraldehyde gives a 3:1 mixture of two erythro aldols. Cleavage of the crude mixture in each case produces solely the *erythro*-α-methyl-β-hydroxy carboxylic acid, identical with a sample synthesized by using reagent 1.[4] Although compound **8** is racemic, the 3:1 diastereomer ratio corresponds to an enantiomer excess (ee) of 50% in acids **15c** and **15e**. Phenylacetaldehyde (**13b**) shows even higher stereoselectivity. The observed diastereomer ratio of 87:13 corresponds to 74% ee. Pivaldehyde gives only a single adduct, within the limits of our analytical method. Thus, we estimate a diastereomer ratio of aldols **14** of at least 19:1, corresponding to at least 90% ee. Diphenylacetaldehyde gives only a single aldol. However, the product from this condensation also contains 10% of an enone (**16**).



16

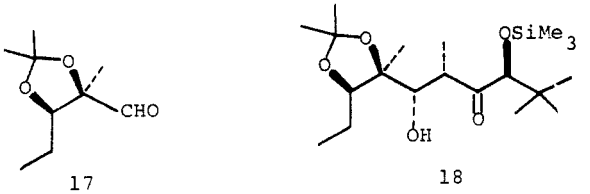
If we assume that all of this enone arises from a minor diastereomeric aldol, then the diastereomer ratio is at least 10:1. However, this is a minimum value and the diastereoface stereoselectivity of **8** with aldehyde **13a** may be much higher than 10:1. There is a clear trend that the diastereoface selectivity of **8** increases as the R group of the aldehyde becomes larger.

The full relative stereochemistry has not been rigorously established for the aldols summarized in Table I. We believe that the major diastereomer in each case has the *3SR,5SR* configuration, since this is the relative stereochemistry which would result from attack on the less hindered face of the enolate double bond in a chelated conformation (eq 1). Support for this hypothesis is pro-



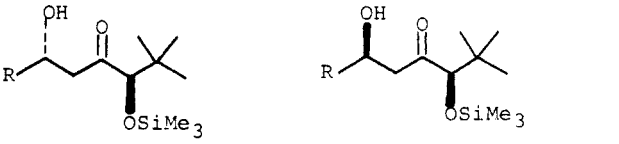
(1)

vided by the condensation of ketone **8** with aldehyde **17**; the full stereostructure of adduct **18** was elucidated by single-crystal X-ray analysis.[5]



17 18

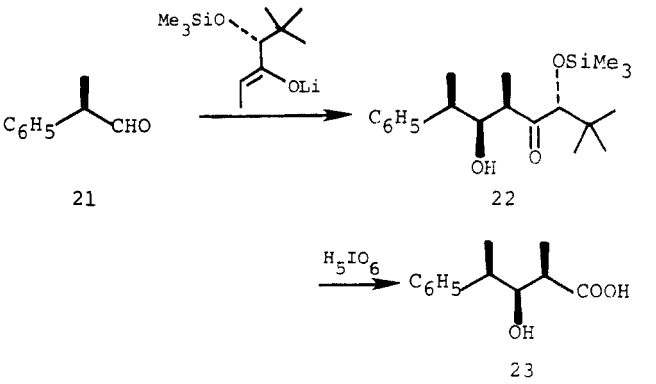
In contrast to the good diastereoface selectivity shown by ketone **8**, the methyl ketone **7** shows no selectivity. Reactions with both benzaldehyde and isobutyraldehyde give 1:1 mixtures of the diastereomeric aldols **19** and **20**.



19a: R = C_6H_5
19b: R = $(CH_3)_2CH$

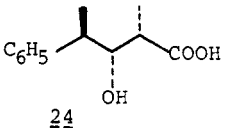
20a: R = C_6H_5
20b: R = $(CH_3)_2CH$

Reaction of compound **8** with racemic α-phenylpropionaldehyde (**21**) affords, within the limits of our analytical tools, a single racemic aldol! Oxidation of this aldol (**22**) affords racemic acid **23**. Suitable control ex-



21 22 23

periments show that acid **23** is at least 98% diastereomerically pure. In particular, isomer **24**, the other erythro

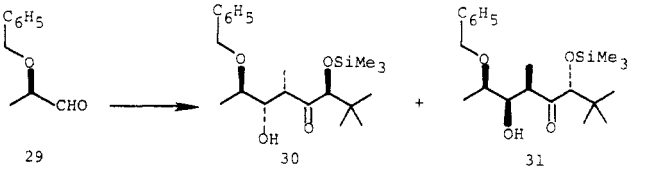


24

diastereomer, would have been detected by our analytical method had it been present to the extent of 2.3 mol %. Thus, the diastereoface selectivity shown by aldehyde **24** in this reaction is >40:1.

A second example of high diastereoface selectivity is seen in the reaction of ketone **8** with the acetonide of racemic glyceraldehde (**25**, Scheme II); a single diastereomer, presumed to be **26**, is produced. Compound **25** reacts with ketone **1** to give two erythro aldols (**27** and **28**) in a ratio of 4.3:1.[5]

Yet another example of abnormally high diastereoface selectivity in a reaction involving ketone **8** is its reaction with *O*-benzyllactaldehyde (**29**), which affords adducts **30** and **31** in a ratio of 5.7:1. With ketone **1**, the two erythro diastereomers **4** and **5** are produced in a ratio of 2:1.

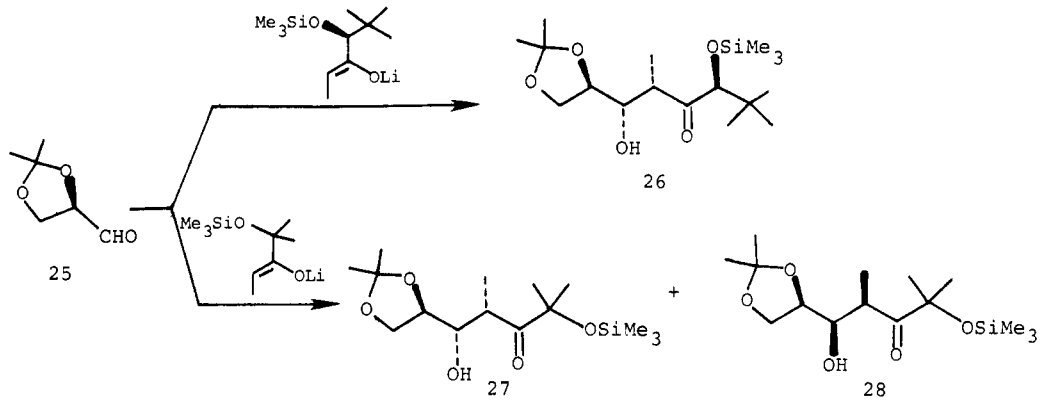


29 30 31

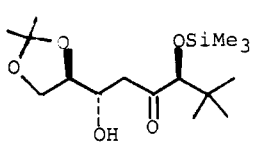
A final example is seen in the previously reported[5] reaction of **8** with racemic aldehyde **17**, which provides isomer **18** as the only isolated aldol, even though aldehyde **17** reacts with ketone **1** to give the two erythro aldols in a ratio of 3:1.

The methyl ketone analogue **7** fails to show the same high diastereoface selectivity in its reactions with chiral

Scheme II



aldehydes. For example, the enolate of (±)-**7** reacts with (±)-**25** to give four racemic aldols (subsequently shown to be **32–35**) in a ratio of 2:2:1:1. Since there are only four



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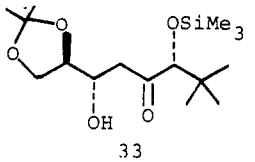

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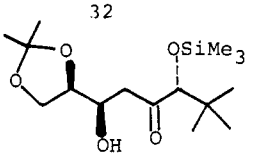

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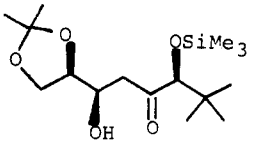


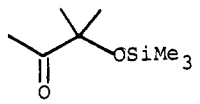
35

possible diastereomers, this ratio shows that neither the aldehyde nor the ketone has an effective diastereoface selectivity in this reaction of more than 2:1. This lack of individual selectivity is shown by the condensation of (±)-**7** with (+)-**25**, which also gives four aldols, enantiomerically pure **32–35**, in the same 2:2:1:1 ratio. Thus, in the cases of (±)-**7** and (±)-**25**, there is no mutual kinetic resolution.

The structures of the four aldols **32–35** were determined by conversion of the mixture into a 2:1 mixture of 2-deoxy-D-ribose (**36**) and 2-deoxy-D-xylose (**37**) by the following sequence: (1) dihydropyran, H^+; (2) $LiAlH_4$; (3) $NaIO_4$, H_2O, EtOH, pH 6.0; (4) 3:2 HOAc–H_2O.[5] Thus the two major diastereomers from the condensation of **7** with **25** must be **32** and **33**, which are eventually transformed into **36**. The ratio (**32** + **33**)/(**34** + **35**) of 2:1 is the same as the diastereoface selectivity shown by aldehyde **25** in its reaction with the achiral methyl ketone **38**.[5] The ratio

36

37



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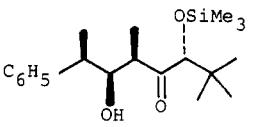
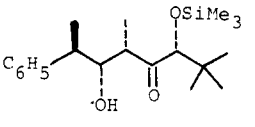
(**32** + **35**)/(**33** + **34**) of 1:1 shows that ketone **7** itself shows no diastereoface selectivity just as in its reactions with benzaldehyde and isobutyraldehyde.

The high degree of mutual kinetic resolution which is displayed in the reactions of racemic **8** with various racemic aldehydes is, at first sight, startling. However, it can be shown that at least some of this mutual kinetic resolution may be anticipated on purely logical grounds as a consequence of the individual diastereoface selectivities of the two reaction partners. To illustrate this point, consider the reaction of racemic ketone **8** with racemic aldehyde **21**. Since the product aldols have four asymmetric carbons, a total of eight racemates is possible. Four of these are erythro and four are threo with respect to the two new centers which are created in the condensation. We may start with the assumption that threo diastereomers may be ignored, since ketones such as **8** have been shown to have erythro/threo kinetic stereoselectivity of about 80:1.[4] The four remaining possibilities are the erythro aldols **22**, **39**, **40**, and **41** (Chart I; note that only one enantiomer is depicted for each racemate). We may make the further assumption that the relative amounts of these four racemates may be *approximated* by using the inherent diastereoface selectivities of the two reaction partners. There is evidence (vide supra) that ketone **8** shows very high diastereoface selectivity with aldehydes having a bulky R group attached to the carbonyl (cf. Table I). Therefore, we shall assume an inherent diastereoface selectivity for **8** of 25:1 for reactions with such aldehydes. Aldehyde **21** usually shows diastereoface selectivity in the range 3:1 to 6:1.[10] However, there is a suggestion that this compound also may show higher diastereoface selectivity with more sterically demanding nucleophiles. For example, the selectivity in the reactions of **21** and various Grignard reagents is 2:1 for CH_3MgBr, 3:1 for C_2H_5MgBr, and >4:1 for C_6H_5MgBr.[11] An example of the same trend with lithium enolates is seen in the reaction of **21** with pinacolone and ethyl *tert*-butyl ketone, where the diastereoface selectivity is 3:1[12] and 6:1,[4] respectively. Thus, we shall

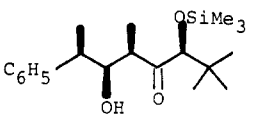
Chart I. Prediction of Diastereomer Ratios for the Reaction of Aldehyde 21 with Ketone 8



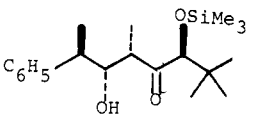
22 (10 × 25 = 250), 87.4%



39 (1 × 1 = 1), 0.4%



40 (10 × 1 = 10), 3.5%



41 (1 × 25 = 25), 8.7%

(10) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, NJ, 1971, pp 90–93.
(11) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

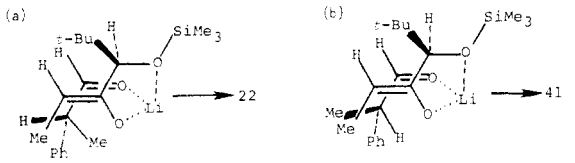


Figure 1. Top view of transition states: (a) (*R*)-**8** + (*R*)-**21** → **22**; (b) (*R*)-**8** + (*S*)-**21** → **41**.

assume an inherent diastereoface selectivity for aldehyde **21** of 10:1 for reactions with the bulky enolates derived from ketones such as **8**. Using these inherent diastereoface selectvities, we may estimate the **22**/**39**/**40**/**41** ratios to be (25 × 10):(1 × 1):(1 × 10):(25 × 1) = 87.4:0.4:3.5:8.7. Thus, the ratio (**22** + **39**)/(**40** + **41**) is predicted to be about 7:1. Note that this is the predicted kinetic resolution in the reaction as both **22** and **39** result from reaction of (*R*)-aldehyde with (*R*)-ketone, while **40** and **41** result from reaction of (*R*)-aldehyde with (*S*)-ketone.

Of course, aldols **22** and **40** both produce acid **23** upon periodic acid oxidation, while aldols **39** and **41** would both produce the erythro, anti-Cram's-rule diastereomer **24**. The approximation being used here predicts that the eventual ratio of **23** to **24** would be (87.4 + 3.5):(0.4 + 8.7) = 10:1, since the multiplicative approach does not change the net diastereoface selectivity shown by either reaction partner. Thus, it is clear that, although the multiplicative approximation accounts for some of the mutual kinetic resolution observed in these double racemic aldol condensations, it does not account for the very high net diastereoface selectivity shown by the aldehydes. However, if there is some other factor which promotes mutual kinetic resolution, then these suprisingly high net diastereoface selectivities can be readily understood. For example, suppose the kinetic resolution in the **8** + **21** reaction is 35:1 instead of 7:1. That is, suppose there is an independent stereoselectivity favoring the reaction (*R*)-**8** + (*R*)-**21** over (*R*)-**8** + (*S*)-**21** by an additional factor of 5. Then the ratio of products (**22** + **39**)/(**40** + **41**) would be 35:1. Note that, in view of the principle of double stereodifferentiation,[1] the ratio of **22** to **39** is expected to be very high (219:1), while the ratio of **40** to **41** is expected to be low (1:2.5). Thus, if mutual kinetic resolution is 35:1, the ratio **22**/**39**/**40**/**41** is expected to be 96.8:0.4:0.8:2.0, and the eventual ratio of acids **23** and **24** is predicted to be 97.6:2.4.

We do not have a convincing rationale as to why the mutual kinetic resolution in these condensations is higher than predicted by the simple multiplicative model. If one assumes that the lithium cation is attracted to all three oxygens in the reacting array, then the probable transition states leading to diastereomers **22** and **41** are those shown in Figure 1. Several other assumptions are also implicit in formulation of the hypothetical transition states depicted in Figure 1. First, we assume that the nucleophile prefers to attack the aldehyde carbonyl anti to the phenyl group.[13] Second, we assume that there is an inherent bias for the aldehyde to react in a conformation in which methyl rather than hydrogen is eclipsed with the carbonyl bond.[14] It is clear from Figure 1 that this inherent bias is amplified by the methyl–methyl interaction in b. This would explain why ketone **8** shows higher inherent diastereoface selectivity than its methyl analogue **7**. However, Figure 1 still does not explain why **21** shows higher diastereoface selectivity with **8** than with ketone **1**, in which the same sort of interactions must be present. It may be a simple matter of reactivity–selectivity. It is clear that ketone **1** is much more reactive than **8**. Consequently, the transition state may be less advanced in reactions with the enolate from ketone **1** than with the enolate from ketone **8**. Thus, the steric effects which partition the reaction between the two transition states depicted in Figure 1 may be much more effective with **8** than with **1**.

Table II. Products from Reaction of a Racemic Aldehyde A with a Racemic Ketone K

reactants	products (ratio)
(*R*)-A + (*R*)-K	(*R*,*R*,*R*)-P″ (*XY*) + (*R*,*S*,*R*)-P″ (1)
(*R*)-A + (*S*)-K	(*R*,*R*,*S*)-P″ (*X*) + (*R*,*S*,*S*)-P″ (*Y*)
(*S*)-A + (*R*)-K	(*S*,*S*,*R*)-P″ (*X*) + (*S*,*R*,*R*)-P″ (*Y*)
(*S*)-A + (*S*)-K	(*S*,*S*,*S*)-P″ (*XY*) + (*S*,*R*,*S*)-P″ (1)

There is one final point which we wish to discuss at this juncture. Although we have a *quantitative* problem in explaining the mutual kinetic resolution shown by (±)-**8** in its reactions with chiral racemic aldehydes, the qualitative trend is clear. This leads us to a postulate which may have considerable generality beyond the aldol condensation: *In reactions involving two chiral, racemic compounds, the magnitude of mutual kinetic resolution depends upon the diastereoselectivity shown by the two reactants in their reactions with achiral reaction partners.* Futhermore, if either reactant in such a combination shows no inherent diastereoselectivity, then mutual kinetic resolution will not be observed, regardless of how stereoselective the other compound is. For example, consider a chiral aldehyde which exists in the enantiomeric forms (*R*)-A and (*S*)-A and a chiral ketone which exists in enantiomeric forms (*R*)-K and (*S*)-K. Chiral aldehyde (*R*)-A can react with an achiral nucleophile to give an alcohol P having a new asymmetric carbon. Two diastereomers are possible, (*R*,*R*)-P and (*R*,*S*)-P. Let the inherent diastereoface selectivity of (*R*)-A in such reactions, (*R*,*R*)/(*R*,*S*), be symbolized by *X*. [Of course, the inherent diastereoface selectivity of (*S*)-A, (*S*,*S*)/(*S*,*R*), is also *X*.] Now, consider the reaction of (*R*)-K with an achiral aldehyde to give an aldol also having a new asymmetric center. Again, two diastereomeric products are possible, (*R*,*R*)-P′ or (*S*,*R*)-P′. Let the inherent diastereoface selectivity of (*R*)-K in such reactions, (*R*,*R*)/(*S*,*R*), be symbolized by *Y*. In the reaction between racemic A and racemic K, four racemic diastereomers of product P″ may be formed, as shown in Table II. Table I also gives the estimated ratios of these four racemates, in terms of factors *X* and *Y*, the inherent stereoselectivities of A and K. Table II shows that the mutual kinetic resolution [the rate of reaction of (*R*)-A with (*R*)-K relative to the rate of reaction of (*R*)-A with (*S*)-K] is equal to the fraction (*XY* + 1)/(*X* + *Y*). Thus, whenever *X* or *Y* = 1, mutual kinetic resolution cannot be observed, even if the other selectivity is very large.

The foregoing discussion explains the behavior of methyl ketone (±)-**7**, which gives the same ratio of aldols **32**–**35** regardless of whether the substrate is (+)-**25** or (±)-**25**. For some inexplicable reason, ketone **7** shows no diastereoface selectivity in its reactions with achiral aldehydes. Thus, it does not display mutual kinetic resolution in its reactions with chiral, racemic aldehydes.

As an application of this chemistry to a specific synthetic problem, we have carried out a synthesis of blastmycinone,[15] a degradation product of the antibiotic antimycin

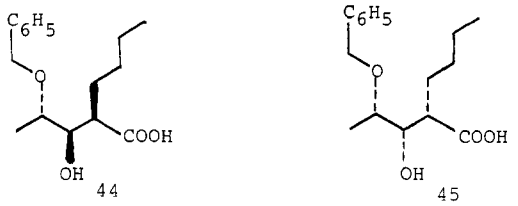
(12) C. T. Buse, Dissertation, University of California, Berkeley, CA, 1978.

(13) (a) M. Chêrest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2201 (1968); (b) N. T. Anh and O. Eisenstein, *Nouv. J. Chim.*, 1, 61 (1977).

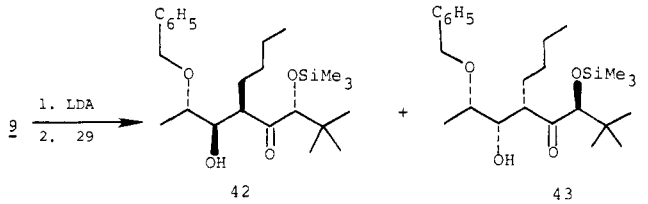
(14) G. J. Karabotsos and N. Hsi, *J. Am. Chem. Soc.*, 87, 2864 (1965).

(15) (a) H. Yonehara and S. Takeuchi, *J. Antibiot., Ser. A*, 11, 254 (1958); (b) M. Kinoshita, S. Aboraki, and S. Umezawa, *J. Antibiot.*, **25**, 373 (1972).

A_3. Condensation of racemic ketone **9** with racemic *O*-benzyllactaldehyde affords two aldols (**42** and **43**)[16] in a ratio of 10:1. These compounds are easily separated and oxidized by periodic acid to acids **44** and **45**, respectively.

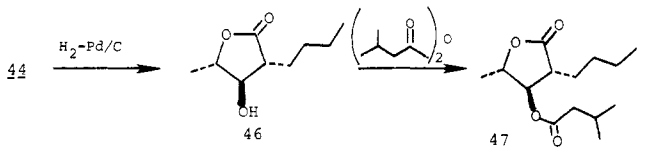


Thus, in its reaction with ketone **9**, aldehyde **29** shows an



effective diastereoface selectivity of 10:1, as compared to 2:1 with ketone **1**. Furthermore, the same type of mutual kinetic resolution is observed in this aldol condensation as is seen in reactions of ketone **8**, although the magnitude is not as great.

Lactone **46** is obtained by catalytic hydrogenolysis of the major hydroxy acid **44**. Esterification of **46** with isovaleric



anhydride affords (±)-blastmycinone (**47**). The overall yield for the four-step synthesis of **47** from ketone **9** is 20%, which compares favorably with the yields obtained in previous syntheses of **47** (16–28%).[17]

In conclusion, we have shown that chiral α-[(trimethylsilyl)oxy] ketones such as **8** and **9** have a useful role in stereoselective synthesis. In addition to showing the high erythro/threo selectivity of ketone **1**,[4] they also show high diastereoface selectivity. Furthermore, several chiral aldehydes show much higher diastereoface selectivity in reactions with **8** and **9** than with ketone **1**. Finally, **8** and **9** show a higher-than-expected degree of mutual kinetic resolution in "double-racemic" condensations with chiral aldehydes. The latter point is of practical significance, since **8** and **9** may therefore be employed for synthesis with racemic substrates.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Ether, 1,2-dimethoxyethane (glyme), and tetrahydrofuran (THF) were distilled from $LiAlH_4$ or 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. UV spectra were determined with a Cary Model 118 ultraviolet spectrophotometer; results are expressed as λ_{max} in nanometers (log ϵ). ^1H NMR spectra were determined on the following spectrometers: Varian T-60, Varian EM390, UCB 180 (a superconducting, 180-MHz, FT instrument), or UCB 250 (a superconducting, 250-MHz, FT instrument). Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Significant ^1H NMR data are tabulated in the following order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) in hertz. ^{13}C NMR spectra were measured at 25.14 MHz with a Nicolet TT-23 spectrometer, at 45.28 MHz on the UCB 180, or at 63.07 MHz on the UCB 250. 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 chromatographs. High-pressure liquid chromatography (HPLC) was done with a Waters Model ALC/GPC-244 liquid chromatograph (analytical) or a Waters PrepLC/System 500 (preparative). μ-Porasil columns were used unless otherwise indicated. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California at Berkeley.

4,4-Dimethyl-3-[(trimethylsilyl)oxy]pentan-2-one (7). To a 1-L, three-necked, round-bottomed flask equipped with a stir bar, dropping funnel, and nitrogen inlet were added THF (155 mL) and ethyl vinyl ether (17.8 mL, 0.19 mol). This solution was cooled to −65 °C and a solution of *tert*-butyllithium in pentane (58.8 mL, 2.0 M, 0.12 mol) was added dropwise. When the addition was complete, the cooling bath was removed and the yellow solution allowed to warm to 20 °C, at which point the color faded. This solution was recooled to −65 °C, and pivaldehyde (12.6 mL, 0.12 mol) in THF (40 mL) was added dropwise. When the addition was complete, the resulting solution was warmed to 0 °C and then poured into 20% aqueous NH_4Cl (400 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 200 mL). The solvent were removed in vacuo, and the residue was stirred with 0.02 N aqueous methanolic HCl for 1 h. Most of the methanol was evaporated and the aqueous residue extracted with ether (4 × 150 mL). The ether extracts were combined and washed with saturated $NaHCO_3$ and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave an oil which was distilled (45 °C, 1.0 torr) to give 6.25 g of the α-hydroxy ketone. This was heated with bis(trimethylsilyl)acetamide (5.8 mL, 0.024 mol) to 100 °C for 12 h. On cooling, the reaction mixture was partitioned between hexanes (150 mL) and water (100 mL). The organic phase was dried ($MgSO_4$) and filtered, and the hexanes were removed in vacuo. The crude product was distilled (40 °C, 1.0 torr) to give 7.50 g (31%) of **7**: IR (film) 2955, 2905, 2870, 1715, 1255, 1100, 1030, 885, 840, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (9 H, s), 0.90 (9 H, s), 2.15 (3 H, s), 3.56 (1 H, s). Anal. Calcd for $C_{10}H_{22}O_2Si$: C, 59.34; H, 10.96. Found: C, 59.60; H, 10.69.

5-Methyl-4-hexen-3-one. In a 2-L, three-necked, round-bottom flask fitted with a mechanical stirrer and a dry ice condenser was placed 500 mL of chloroform. Propionyl chloride (174 mL, 2 mol) was added, the solution was cooled in an ice bath, and aluminum chloride (466 g, 2 mol) was added in portions. After the solution was again cooled, isobutylene was condensed into the reaction mixture at the rate of 1 drop/s for 1 h. The cooling bath was removed and the solution stirred for 3 h. The reaction mixture was poured onto a mixture of 1 kg of ice and 2 L of 10% HCl. The layers were separated, and the aqueous phase was extracted with chloroform (3 × 500 mL). The combined organic phases were washed with 10% HCl (2 × 600 mL) and dried ($MgSO_4$). Filtration and removal of the solvents in vacuo gave approximately 500 mL of a red oil. This material was added slowly to a hot solution of 276 g of K_2CO_3 in 1 L of water. After the addition, the solution was heated at reflux for 2 h and then cooled. The condenser was replaced with a Claisen head, and the steam-volatile materials were removed by azeotropic distillation. The resulting two-phase distillate was saturated with solid NaCl and the organic phase separated. Drying ($MgSO_4$) and distillation at 115 torr through a 15-cm Vigreux column provided 90 g (40%) of the known[8] enone, bp 115–125 °C. VPC (8% SE-30, 130 °C)

(16) Like all the compounds in this paper, compounds **42–47** are racemic. We depict here the enantiomeric series which corresponds to the absolute configuration of naturally derived blastmycinone.

(17) M. Kinoshita, S. Aburaki, M. Wada, and S. Umezawa, *Bull. Chem. Soc. Jpn.*, **46**, 1279 (1973).

(18) This is a modification of the procedure of B. Pressman, L. Anderson, and H. Lardy, *J. Am. Chem. Soc.*, **72**, 2404 (1950).

(19) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 463 (1939).

showed this was >95% pure. The enone was stabilized with hydroquinone and stored in a refrigerator.

2,2-Dimethyl-3-[(trimethylsilyl)oxy]-4-hexanone (8). Method A. To a 1-L, three-necked, round-bottomed flask was added 28.56 g of CuI (149.9 mmol) which had been purified by extraction with THF, followed by drying in vacuo. The flask was fitted with a nitrogen inlet and a 250-mL, pressure-equalizing dropping funnel, and 250 mL of anhydrous ether was added. The flask was then cooled in an ice bath, and methyllithium (200 mL of a 1.50 M solution, 0.3 mol) was transferred into the dropping funnel. The cuprate reagent was formed by dropwise addition of the methyllithium solution to the cooled mixture. After 10 min, the neat enone (16.80 g, 18.9 mL, 150 mmol) was added dropwise, followed by triethylamine (23 mL, 165 mmol) and, with rapid magnetic stirring, chlorotrimethylsilane (21 mL, 165 mmol). After the mixture was stirred for 30 min, the bath was removed, and the reaction mixture was poured into a mixture of 500 mL of ice-cold 5% HCl and 250 mL of petroleum ether. When gas evolution subsided, this two-phase system was filtered through a pad of Celite to remove the copper salts. The layers were separated, and the aqueous phase was extracted with ether (2 × 300 mL). The combined organic layers were washed with $NaHCO_3$ (500 mL) and NaCl (500 mL), dried (K_2CO_3), and filtered, and the solvents were removed in vacuo to give 24 g of crude enol silyl ether as a 2:1 mixture of stereoisomers (VPC, NMR). This material was utilized without further purification.

In a 1-L, round-bottomed flask was dissolved 85% *m*-chloroperoxybenzoic acid (25 g, 123 mmol) in 250 mL of CH_2Cl_2, and the mixture was cooled to 0 °C. The crude enol ether in 100 mL of CH_2Cl_2 was added dropwise over 1 h, and the reaction mixture was allowed to stand an additional hour. Two possible workup procedures follow.

(1) The solvents were removed in vacuo, and the residue was partitioned between 10% HCl (100 mL) and ether (300 mL) for 3 h. The layers were separated, and the aqueous phase was extracted with 100 mL of ether. The combined organic phases were washed with 5% NaOH (3 × 75 mL), $Na_2S_2O_3$ (100 mL), 1% HCl (100 mL), $NaHCO_3$ (2 × 100 mL), and NaCl (100 mL). Drying ($MgSO_4$), filtering, removal of solvents in vacuo, and distillation provided 12.19 g (56%) of hydroxy ketone **11**. A mixture of 574 mg (3.98 mmol) of this material and 405 mg (1.99 mmol) of bis(trimethylsilyl)acetamide was heated at 150 °C for 24 h. The mixture was cooled and poured into a mixture of water and pentane. The pentane layer was separated and washed with water, dried ($MgSO_4$), and evaporated to give 450 mg (52%) of a colorless liquid: bp (bath temperature) 90–100 °C (18 mm); ^1H NMR (CCl_4) δ 3.59 (1 H, s, methine H), 2.47 (2 H, q, J = 7, methylene H's), 1.03 (3 H, d, J = 7, methyl H's), 0.90 (9 H, s, *t*-Bu H's). Anal. Calcd for $C_{11}H_{24}O_2Si$: C, 61.05; H, 11.18. Found: C, 60.96; H, 10.90.

(2) The solids were removed by filtration, and the solution was washed with 5% NaOH (2 × 100 mL), $Na_2S_2O_3$ (100 mL), and NaCl (100 mL). Drying ($MgSO_4$), filtering, removal of solvents in vacuo, and fractional distillation through a 15-cm Vigreux column provided 13.05 g (40% overall) of the silyloxy ketone.

Method B. A solution of 3.74 mL (2.88 g, 40 mmol) of 1-methoxypropene (mixture of *E* and *Z* isomers) and 3.06 mL (2.35 g, 20 mmol) of tetramethylethylenediamine in 10 mL of pentane was cooled to −70 °C, and 12.5 mL of a 1.6 M solution of *tert*-butyllithium (20 mmol) in pentane was slowly dropped in. The mixture was allowed to warm to room temperature for 1 h. The homogeneous solution which resulted was cooled to −70 °C, and 2.17 mL (1.72 g, 20 mmol) of pivaldehyde was added at a rate such that the temperature did not rise above −60 °C. After the addition was complete, the solution was allowed to warm to room temperature and was poured into water. The layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were evaporated, and the residue was treated with 100 mL of 0.1 N methanolic HCl containing an additional 10 drops of concentrated HCl for 30 min. Most of the methanol was evaporated, and the product was extracted with ether. The ether extracts were dried (Na_2SO_4) and evaporated. Distillation of the residue gave 1.56 g (54%) of a colorless oil: bp 100 °C (17 torr); ^1H NMR (CCl_4 plus trace of HCO_2H) δ 3.75 (1 H, s), 2.52 (2 H, m), 1.08 (3 H, t, J = 7), 0.97 (9 H, s); IR (film) 3475, 1705, 1085 cm^{-1}. The hydroxy ketone was silylated with bis(trimethylsilyl)acetamide as outlined in procedure A above.

2,2-Dimethyl-3-hydroxy-4-nonanone (12). To a solution of 3.75 g (19.7 mmol) of 2-pentyl-1,3-dithiane in 50 mL of THF at −40 °C was added over a 4-min period 12.5 mL (20.8 mmol) of a 1.66 M solution of *n*-BuLi in hexane. The solution was stirred for 2 h at −20 °C, after which time it was cooled to −70 °C, and 2.14 mL (1.69 g, 19.7 mmol) of pivaldehyde was added at such a rate as to keep the temperature of the mixture below −65 °C. After being stirred for 45 min at −70 °C, the reaction mixture was poured into 150 mL of water and extracted with dichloromethane. The organic extracts were washed with water, 7% aqueous KOH, and again with water and then dried over K_2CO_3. Evaporation of the solvents left 5.98 g of a yellow oil which was distilled to give 4.64 g (85%) of the desired adduct as a pale yellow liquid: bp 123–126 °C (3.6 torr); IR (film) 3450, 1010, 910 cm^{-1}; ^1H NMR (CCl_4) δ 0.88 (3 H, t, J = 6), 1.12 (9 H, s), 1.17–2.13 (10 H, m), 2.40–3.17 (4 H, m), 2.90 (1 H, s), 3.60 (1 H, s). An analytical sample was obtained by preparative TLC on silica gel, eluting with 15% ether/hexane. Anal. Calcd for $C_{14}H_{28}OS_2$: C, 60.82; H, 10.21; S, 23.19. Found: C, 60.98; H, 10.23; S, 23.24.

A suspension of 4.21 g (15.2 mmol) of 2-(2,2-dimethyl-1-hydroxypropyl)-2-pentyl-1,3-dithiane in 100 mL of 4:1 acetonitrile–water was added to a rapidly stirred suspension of 9.00 g (33.1 mmol) of $HgCl_2$ and 1.00 g (10.0 mmol) of $CaCO_3$ in 150 mL of 4:1 acetonitrile–water under nitrogen. The mixture was heated at reflux for 5 h, during which time a thick white precipitate formed. The reaction mixture was then filtered through a pad of Celite, and the filter pad was washed well with 1:1 hexane–dichloromethane. The organic extracts were washed with 5 M NH_4OAc, water, and brine and dried over $MgSO_4$. Evaporation of the solvent left 2.99 g of a cloudy yellow liquid. The crude product was purified by column chromatography on silica gel, eluting with 20% ether/hexane, to yield 1.99 g (71%) of the desired hydroxy ketone as a pale yellow liquid: IR (film) 3480, 1710 cm^{-1}; ^1H NMR (CCl_4) δ 0.87 (3 H, m), 0.93 (9 H, s), 1.10–1.73 (6 H, m), 2.45 (2 H, m), 3.47 (1 H, d, J = 7), 3.63 (1 H, d, J = 7). Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.91. Found: C, 70.88; H, 11.67.

2,2-Dimethyl-3-[(trimethylsilyl)oxy]-4-nonanone (9). A mixture of 1.81 g (9.72 mmol) of hydroxy ketone **12** and 1.80 mL (1.48 g, 7.28 mmol) of bis(trimethylsilyl)acetamide was stirred under an atmosphere of N_2 at 75–105 °C for 15 h. The reaction mixture was taken uup in 30 mL of hexane, washed with water, and dried over $MgSO_4$. Evaporation of the solvent left 2.20 g of a pale yellow liquid. The crude product was purified by column chromatography on silica gel, eluting with 15% ether/hexane, to yield 2.02 g (80%) of the desired silyloxy ketone as a clear colorless liquid: IR (film) 1705, 1250 cm^{-1}; ^1H NMR (CCl_4) δ 0.09 (9 H, s), 0.71–1.01 (3 H, m), 0.81 (9 H, s), 1.07–1.67 (6 H, m), 2.41 (2 H, m), 3.51 (1 H, s). An analytical sample was prepared by preparative GLC using an 8-ft, 10% SE-30 column at 200 °C. Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.07; H, 11.70. Found: C, 64.84; H, 11.53.

General Procedure for Aldol Condensation and Periodic Acid Cleavages Using Ketone 8. Aldol Condensation. To a solution of LDA (2.25 mmol, prepared from 0.32 mL of diisopropylamine and 1.50 mL of a 1.50 M solution of *n*-BuLi in hexanes) in 7 mL of THF at −70 °C was added ketone **8** (0.49 mL, 2.00 mmol). After the mixture was stirred for 2 h, TMEDA (0.60 mL, 4.03 mmol) was added followed by the aldehyde (2.00 mmol). After the indicated reaction time, the reaction was quenched by the addition of 4 mL of saturated $NaHCO_3$. The layers were separated, the aqueous phase was extracted (2 × 15 mL ether), and the combined organic phases were washed with 1% HCl and NaCl (10 mL each). Drying ($MgSO_4$), filtering, and removal of solvents in vacuo provided the crude reaction mixture which was analyzed by ^{13}C NMR.

Periodic Acid Oxidation. The hydroxy ketone **14** (2.00 mmol) was dissolved in 15 mL of methanol, and periodic acid (8 mL of a 1 M solution, 8.00 mmol) was added. The reaction mixture was stirred for the indicated time, and most of the solvents were removed in vacuo. The residue was partitioned between water and ether, the layers were separated, and the aqueous phase was extracted with ether (2 × 15 mL). The combined organic phases were extracted with 5% NaOH (2 × 20 mL), and the resulting aqueous phases were acidified with concentrated HCl. Ether

Table III

fraction	wt, mg	identity	fraction	wt, mg	identity
1	63	ketone 8a	3	571	adduct 14a
2	130	aldehyde 13a	4	80	enone 16

Table IV

fraction	wt, mg	identity	fraction	wt, mg	identity
1	83	ketone 8b	3	315	adduct 14b
2	42	aldehyde 13b			

extraction (3 × 20 mL), washing with $Na_2S_2O_3$ and NaCl solutions (10 mL each), drying, filtering, and removal of solvents in vacuo provided the essentially pure product.

***erythro*-1,1-Diphenyl-3,6,6-trimethyl-2-hydroxy-5-[(trimethylsilyl)oxy]-4-heptanone (14a).** Aldol condensation using the general procedure (reaction time 20 min) provided in quantitative yield a material which was 80% condensed and more than 90% a single stereoisomer. Preparative HPLC (15% ether/hexane) gave four fractions with 100% recovery of material (see Table III). Fraction 3 gave the following spectra: ^{1}H NMR ($CDCl_3$) δ 0.08 (9 H, s), 0.82 (9 H, s), 1.17 (3 H, d, J = 7), 3.00 (1 H, br q, J = 7), 3.55 (1 H, br s), 3.68 (1 H, s), 4.03 (1 H, d, J = 12), 4.72 (1 H, br d, J = 12), 7.27 (10 H, br s); ^{13}C NMR δ 219.8, 129.4, 129.1, 128.8, 128.4, 128.2, 126.4, 85.7, 71.7, 54.9, 41.5, 35.5, 26.5, 9.5, 0.3. Upon refrigeration, this material slowly crystallized. Recrystallization from hexane gave material (mp 73–74 °C) which showed identical NMR spectra with those listed above. Anal. Calcd for $C_{25}H_{36}O_3Si$: C, 72.73; H, 8.73. Found: C, 72.79; H, 8.85.

***erythro*-4,4-Diphenyl-3-hydroxy-2-methylbutanoic Acid (15a) and Its Methyl Ester.** The standard procedure was followed (reaction time 18 h) to give the acid as a foam. A small sample (10 mg) was obtained in crystalline form, mp 146 °C (from hexane). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.26; H, 6.68. To facilitate isolation, the acid was esterified with excess ethereal diazomethane to give the methyl ester in 84% overall yield. This material was shown by ^{1}H NMR to be the erythro isomer by comparison with an authentic mixture of the erythro and threo isomers prepared by condensation of the lithium enolate of methyl propionate with diphenylacetaldehyde: ^{1}H NMR ($CDCl_3$) δ 1.20 (3 H, d, J = 7), 2.50 (2 H, m), 3.55 (3 H, s), 3.90 (1 H, d, J = 10), 4.85 (1 H, dd, J = 10, 3), 7.17 (10 H, br s); ^{13}C NMR δ 175.5, 141.7, 141.5, 128.8, 128.6, 128.2, 126.8, 73.3, 55.4, 51.7, 41.7, 9.4.

***erythro*-1-Phenyl-3,6,6-trimethyl-5-[(trimethylsilyl)oxy]-2-hydroxy-4-heptanone (14b).** Aldol condensation under standard conditions (reaction time 25 min) gave in 100% yield a material which was >90% a single stereoisomer and was 75% condensed. Preparative HPLC gave three fractions (see Table IV). Adduct **14b** gave the following spectra: ^{1}H NMR ($CDCl_3$) δ 0.13 (9 H, s), 0.83 (9 H, s), 1.16 (3 H, d, J = 7), 2.71 (1 H, br q, J = 7), 3.00 (2 H, br d, J = 2), 3.65 (1 H, s), 4.00 (1 H, dt, J = 2, 7); ^{13}C NMR δ 129.2, 128.5, 126.4, 86.2, 72.0, 43.4, 40.2, 26.5, 10.5, 0.4. Upon being allowed to stand in a refrigerator, this material slowly crystallized. Recrystallization from hexane gave material (mp 56–58 °C) which showed identical NMR spectra with those listed above. Anal. Calcd for $C_{19}H_{32}O_3Si$: C, 67.81; H, 9.58. Found: C, 67.93; H, 9.28.

***erythro*-4-Phenyl-3-hydroxy-2-methylbutanoic Acid (15b).** The standard procedure was followed (reaction time 48 h) to give the known[4] acid in 62% yield.

***erythro*-2,2,5,7-Tetramethyl-3-[(trimethylsilyl)oxy]-6-hydroxy-4-octanone (14c).** Aldol condensation (reaction time 25 min) using the general procedure gave in 93% yield a material which was a 3:1 mixture of stereoisomers: ^{1}H NMR ($CDCl_3$) δ 0.20 (9 H, s), 0.98 (9 H, s), 3.33 (1 H, m), 3.77 (1 H, s); ^{13}C NMR, major δ 218.6, 85.0, 74.4, 40.1, 34.1, 25.3, 18.3, 17.4, 8.7, –1.0; minor δ 218.6, 85.0, 74.4, 40.1, 34.5, 25.3, 18.7, 17.9, 8.5, –0.5. Preparative GLC (8% SE-30, 170 °C) gave the analytical sample. Anal. Calcd for $C_{15}H_{32}O_3Si$: C, 62.45; H, 11.18. Found: C, 62.56; H, 10.96.

***erythro*-2,4-Dimethyl-3-hydroxypentanoic Acid (15c).** The standard procedure was followed (reaction time 48 h) to give the known[4] acid in 45% overall yield.

***erythro*-2,2,5,7,7-Pentamethyl-3-[(trimethylsilyl)oxy]-6-hydroxy-4-octanone (14d).** Aldol condensation (reaction time 35 min) using the general procedure gave in 74% yield a material which was shown by ^{13}C NMR to be a starting ketone and a single product in a 2:3 ratio. Preparative GLC gave a pure sample: 58 mg (9%); ^{1}H NMR ($CDCl_3$) δ 0.16 (9 H, s), 0.83 (9 H, s), 0.93 (9 H, s), 1.06 (3 H, d, J = 7), 3.33 (1 H, s), 3.66 (1 H, s). The ^{13}C NMR spectrum of this material showed the pure adduct in addition to three small peaks not present in the crude material. These peaks correspond to a new isomer to which we assign a structure which has the silyl group at the aldol oxygen. The GLC-collected sample appeared to contain 13% of this new isomer. It was shown by desilylating (MeOH/HCl) a sample of this adduct that this minor isomer was not simply the dihydroxy ketone: ^{13}C NMR δ 219.6, 85.9 (85.4), 76.4, 41.2 (42.8), 35.6, 27.2, 26.7, 11.3 (10.4), 0.5. Anal. Calcd for $C_{16}H_{34}O_3Si$: C, 63.52; H, 11.33. Found: C, 63.65; H, 11.26.

***erythro*-2,4,4-Trimethyl-3-hydroxypentanoic Acid (15d).** The standard procedure was followed (reaction time 48 h) to give the erythro acid **20** in 57% yield: IR (CCl_4) 3640, 3530, 2950, 1715, 1460, 1430, 1360, 1320, 1250, 1160, 1050, 940, 920, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (9 H, s), 1.20 (3 H, d, J = 7), 2.66 (1 H, dq, J = 3, 7), 3.62 (1 H, d, J = 3); ^{13}C NMR δ 78.0, 41.0, 26.5, 12.5; mp (from hexane) 115–116 °C. Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.62; H, 9.77.

(1*RS*,4*RS*)- and (1*SR*,4*RS*)-Dimethyl-4-[(trimethylsilyl)oxy]-1-phenyl-1-hydroxyhexan-3-ones (19a and 20a). To a 100-mL, three-necked, round-bottomed flask with a stir bar, nitrogen inlet, and thermometer were added THF (17.5 mL) and diisopropylamine (0.70 mL, 5 mmol). This was cooled to 0 °C, and a solution of *n*-butyllithium in hexanes (3.15 mL, 1.59 M, 5 mmol) was added in one portion. After being stirred 5 min, the mixture was cooled to –78 °C, and ketone **7** (1.01 g, 5 mmol) was added dropwise. This mixture was stirred for 2 h at –78 °C. Benzaldehyde (0.53 mL, 5 mmol) was added in one portion and the mixture stirred 20 min. The reaction was quenched with saturated $NaHCO_3$ (15 mL) and the mixture allowed to warm to room temperature. The layers were separated, the aqueous phase was extracted with ether (2 × 50 mL), and the combined organic fractions were washed with cold 1% HCl, saturated $NaHCO_3$, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave 1.10 g (71%) of a 1:1 mixture of **19a** and **20a**. An analytical sample was prepared by preparative TLC using 40% ether in hexanes as the eluant (R_f 0.27): IR (film) 3500, 2950, 1950, 1880, 1810, 1710, 1240, 1100, 890, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.10 (9 H, s), 0.90 (9 H, s), 2.90 (2 H, m), 3.60 (1 H, s), 5.10 (1 H, m), 7.35 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 128.5, 127.5, 125.8, 86.2, 85.9, 69.9, 48.2, 26.3, –0.1; mass spectrum, 234 (1.1), 159 (88.0), 129 (31.4), 106 (67.1), 73 (100.0). Anal. Calcd for $C_{17}H_{28}O_3Si$: C, 66.19; H, 9.15. Found: C, 66.28; H, 8.91.

(3*RS*,6*RS*)- and (3*RS*,6*SR*)-2,2,7-Trimethyl-6-hydroxy-3-[(trimethylsilyl)oxy]octan-4-ones (19b and 20b). To a 100-mL, three-necked, round-bottomed flask with a stir bar, nitrogen inlet, and thermometer were added THF (17.5 mL) and diisopropylamine (0.70 mL, 5 mmol). This was cooled to 0 °C and *n*-butyllithium (3.15 mL of a 1.59 M solution in hexanes, 5 mmol) was added in one portion. After being stirred 5 min, the mixture was cooled to –78 °C, and ketone **7** (1.01 g, 5 mmol) was added dropwise. This was stirred for 2 h at –78 °C, isobutyraldehyde (0.45 mL, 5 mmol) was added in one portion, and the mixture was stirred 20 min. The reaction was quenched with saturated $NaHCO_3$ (15 mL) and the mixture allowed to warm to room temperature. The layers were separated, the aqueous phase was extracted with ether (2 × 50 mL), and the combined organic fractions were washed with cold 1% HCl, saturated $NaHCO_3$, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave 0.86 g (63%) of a 1:1 mixture of **19b** and **20b**: IR (film) 3500, 2950, 1700, 1480, 1250, 890, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.10 (9 H, s), 0.95 (9 H, s), 1.70 (1 H, m), 2.10–3.40 (3 H, complex), 3.60 (1 H, s), 3.70 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 216.7, 216.1, 86.0, 85.7, 72.0, 71.8, 42.6, 35.2, 35.0, 33.5, 33.0, 26.1, 17.8, 17.5, 0.0.

Attempted preparation of an analytical sample by column chromatography on silica gel (E. Merck) with 40% ether in hexanes as the eluant resulted in loss of the trimethylsilyl group. A satisfactory analysis was obtained on the diol: IR (film) 3425, 2950, 1700, 1460, 1360, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (15

H, m), 1.65 (1 H, septet, J = 7), 2.2–3.8 (6 H, complex). Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.60; H, 10.80.

(3*SR*,5*SR*,6*RS*,7*SR*)-7-Phenyl-6-hydroxy-2,2,5-trimethyl-3-[(trimethylsilyl)oxy]octan-4-one (22). To a 50-mL, three-necked, round-bottomed flask with a stir bar, nitrogen inlet, and low-temperature thermometer were added THF (7.0 mL) and diisopropylamine (0.48 mL, 3.43 mmol). This was cooled to 0 °C, and *n*-butyllithium (2.20 mL of a 1.50 M solution in hexanes, 3.30 mmol) was added in one portion. This was cooled to −70 °C, and ketone **8** (0.65 g, 3.0 mmol) was added dropwise. After the mixture was stirred 2 h, TMEDA (0.90 mL, 6.05 mmol) was added, neat, followed by 2-phenylpropionaldehyde (0.40 g, 3.00 mmol), and the mixture was stirred 20 min. The reaction was quenched with saturated $NaHCO_3$ (1 mL) and the mixture allowed to warm to room temperature with stirring. The layers were separated, the aqueous phase was extracted with ether (3 × 25 mL), and the combined organic phases were washed with cold 1% HCl, saturated aqueous $NaHCO_3$, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave 644 mg of crude **22** which was purified by preparative HPLC with 10% ether in hexanes as the eluant to give 572 mg (54%) of pure **22**:[20] IR (film) 3500, 2950, 1690, 1450, 1250, 1090, 880, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (9 H, s), 0.80 (9 H, s), 1.10 (3 H, d, J = 7), 1.50 (3 H, d, J = 6), 2.80 (2 H, m), 3.6 (3 H, m), 7.20 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 219.2, 143.8, 128.3, 128.0, 127.5, 127.3, 126.4, 85.4, 74.8, 42.8, 41.4, 26.2, 18.6, 9.5, 0.0. Anal. Calcd for $C_{20}H_{34}O_3Si$: C, 68.52; H, 9.78. Found: C, 68.68; H, 9.88.

In other experiments, we obtained higher condensation yields. In our best run, on a 1.0-mmol scale, we obtained (after preparative HPLC) 80% of aldol **22**, 19% of ketone **8**, and 19% of aldehyde **21**. The stereochemical homogeneity of aldol **22** was demonstrated by ^{13}C NMR under conditions when we could have detected approximately 2% of another stereoisomer (TT-23, 16-h spectrum, 1.0 M solution).

(2*SR*,3*RS*,4*SR*)-Phenyl-3-hydroxy-2-methylpentanoic Acid (23). To a solution of **22** (380 mg, 1.08 mmol) in methanol (8 mL) was added a solution of H_5IO_6 (1.04 g, 4.56 mmol) in water (4 mL), and the mixture was stirred overnight. Most of the methanol was removed in vacuo and the aqueous residue extracted with ether (3 × 15 mL). The combined ether fractions were extracted with 5% aqueous NaOH (2 × 20 mL). The NaOH extracts were acidified with concentrated HCl and extracted with ether (3 × 20 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), and filtered, and the ether was removed in vacuo to give 194 mg (80%) of **23**. An analytical sample was prepared by recrystallization from ether/hexanes: mp 134–135 °C; IR (Nujol mull) 3360, 1700, 1205, 1120, 965 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (3 H, d, J = 7), 1.35 (3 H, d, J = 6), 2.25 (1 H, m), 2.75 (1 H, m), 4.05 (1 H, dd, J = 2, 8), 7.1 (5 H, m); ^{13}C NMR (CD_3COCD_3) δ 127.9, 127.5, 126.9, 126.5, 125.2, 74.8, 42.3, 40.9, 16.7, 8.4. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.86; H, 7.78.

The stereochemical homogeneity of acid **23** was shown by ^{13}C NMR under conditions where we could have detected 2% of another stereoisomer. Thus, the ^{13}C NMR spectrum of an authentic mixture consisting of 97.7% **23** and 2.3% **24** clearly showed the resonances due to **24**. Under the same ^{13}C NMR conditions, the sample of **23** prepared by the foregoing procedure showed no **24**.[21]

(±)-Glyceraldehyde Acetonide[18] (25). To a 2-L, round-bottomed flask was added sorbitol (85 g, 467 mmol) and $ZnCl_2$ (135 g, 991 mmol) in dry acetone (675 mL), and the mixture was stirred for 4 h. The mixture was poured into a rapidly stirring solution of K_2CO_3 (170 g) in water (170 mL) layered with ether (675 mL). The mixture was stirred for 20 min and then filtered. The salts were washed with a 1:1 mixture of acetone and ether (400 mL), the combined filtrates were dried (K_2CO_3) and filtered, and the solvents were removed in vacuo. The crude reaction mixture was placed in a 2-L, round-bottom flask and refluxed with heptane (800 mL) for 3 h. When the mixture cooled, the supernatant was decanted and the heptane removed in vacuo to give 56.5 g of an oil which partly solidified on exposure to high vacuum overnight. This was recrystallized from hot di-*n*-butyl ether to give 6.64 g of the 1,2:5,6-diacetonide of soribitol: mp 95–95.5 °C (lit. 95–95.5 °C); IR (Nujol mull) 3350, 1460, 1370, 1240, 1215, 1110, 1060, 840, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (3 H, s), 1.43 (3 H, s), 1.46 (3 H, s), 1.50 (3 H, s), 2.62 (1 H, s), 2.70 (1 H, s), 2.79 (1 H, s), 2.85 (1 H, s), 4.0 (6 H, m). Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.97; H, 8.46. Found: C, 54.78; H, 8.33.

To a solution of the above acetonide (1.5 g, 5.7 mmol) in dry benzene (20 mL) was added $Pb(OAc)_4$ (2.53 g, 5.7 mmol), the mixture was filtered through a pad of Celite, and the solvent was removed in vacuo at 10 °C. To this was added CCl_4 (50 mL), and the evaporation was repeated. The crude material was distilled by Kugelrohr (≤40 °C, 1.5 torr) to give 1.0 g (67%) of (±)-**25** whose spectral properties (IR, ^1H NMR) were identical with those of the (+) enantiomer;[19] $[\alpha]^{25}_D$ 0° (*c* 0.5, $CHCl_3$).

(3*SR*,5*SR*,6*SR*,7*SR*)-7,8-*O*-Isopropylidene-6,7,8-trihydroxy-2,2,5-trimethyl-3-[(trimethylsilyl)oxy]octan-4-one (26). To a 100-mL, three-necked round-bottomed flask with a stir bar, thermometer, and nitrogen inlet were added THF (17.5 mL) and diisopropylamine (0.77 mL, 5.5 mmol), and the solution was cooled to 0 °C. To this was added *n*-butyllithium (3.93 mL of a 1.40 M solution in hexanes, 5.5 mmol) in one portion. After being stirred 5 min, the mixture was cooled to −78 °C, and ketone **8** (1.08 g, 5 mmol) was added dropwise. This was stirred 2 h, and TMEDA (1.54 mL, 10 mmol) was added followed by (±)-**25** (0.65 g, 5.0 mmol), neat, dropwise. After the mixture was stirred 20 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (5.0 mL) and the mixture allowed to warm to room temperature. The layers were separated, the aqueous phase was extracted with ether (2 × 50 mL), and the combined organic fractions were washed with cold 1% HCl, saturated $NaHCO_3$, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave the crude product which was chromatographed on silica gel (E. Merck) with 10% ether in hexanes as the eluant to furnish 1.10 g (63%) of pure **26**: IR ($CHCl_3$) 3450, 2950, 1700, 1370, 1250, 1060, 840 cm^{-1}; ^1H NMR ($CDCl_3$) 0.15 (9 H, s), 0.95 (9 H, s), 1.15 (3 H, d, J = 8), 1.35 (6 H, s), 3.20–4.15 (5 H, complex multiplets); ^{13}C NMR ($CDCl_3$) δ 220.9, 109.6, 86.5, 72.2, 67.6, 40.9, 35.4, 26.6, 25.1, 10.5, 0.5. Anal. Calcd for $C_{17}H_{34}O_5Si$: C, 58.92; H, 9.89. Found: C, 59.30; H, 10.08.

2-(Benzyloxy)propanal (29). To a solution of 4.38 g (22.6 mmol) of methyl 2-(benzyloxy)propionate in 100 mL of ether at −100 °C was added dropwise over 30 min 45.0 mL (45.0 mmol) of a 1 M solution of diisobutylaluminum hydride in hexane. The reaction mixture was stirred for 1 h at −100 °C, after which it was transferred rapidly by cannula into 200 mL of a rapidly stirred 10% aqueous HCl solution. The quenched reaction mixture was extracted with ether, and the ether extracts were washed with water and dried over $MgSO_4$. Evaporation of the solvent gave 3.28 g of the crude aldehyde, which after bulb-to-bulb distillation [80 °C (bath temperature), 0.3 torr] yielded 2.88 g (78%) of the aldehyde as a clear colorless liquid having physical properties consistent with those reported elsewhere.[17]

(3*SR*,5*SR*,6*SR*,7*RS*)- and (3*RS*,5*RS*,6*RS*,7*RS*)-7-(Benzyloxy)-6-hydroxy-2,2,5-trimethyl-3-[(trimethylsilyl)oxy]-4-octanones (30 and 31). Condensation under the standard conditions (reaction time 30 min) on a 1-mmol scale gave 0.293 g (78%) of the crude aldol as a 6:1 mixture of diastereomers. The crude product was chromatographed on silica, eluting with 10% ether/hexane, to yield 0.113 g (30%) of the pure aldol: IR (film) 3500, 1690, 1250 cm^{-1}; ^1H NMR (CCl_4) δ 0.33 (9 H, s), 0.97 (3 H, m), 1.07 (9 H, s), 1.37 (3 H, d, J = 6), 3.13 (1 H, br s), 3.23–3.63 (3 H, m), 3.70 (1 H, s), 4.33 (1 H, d, J = 12), 4.65 (1 H, d, J = 12), 7.26 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 128.3, 127.8, 86.2 (major), 85.6 (minor), 74.0, 73.7, 70.6, 40.8, 35.5, 26.6, 16.3 (major), 16.0 (minor), 11.1 (minor), 10.4 (major), 0.4 (major), 0.3 (minor). Anal. Calcd for $C_{21}H_{36}O_4Si$: C, 66.27; H, 9.53. Found: C, 66.34; H, 9.42.

(3*SR*,6*SR*,7*RS*)-, (3*RS*,6*SR*,7*RS*)-, (3*RS*,6*RS*,7*RS*)-, and (3*SR*,6*RS*,7*RS*)-6,7-*O*-Isopropylidene-5,6,7-trihydroxy-3-[(trimethylsilyl)oxy]-2,2-dimethylheptan-4-ones (32–35). To a 100-mL, three-necked, round-bottomed flask with a stir bar, thermometer, and nitrogen inlet were added THF (17.5 mL) and diisopropylamine (0.77 mL, 5.5 mmol), and the solution was cooled to 0 °C. To this was added *n*-butyllithium (3.93 mL of a 1.40 M solution in hexanes, 5.5 mmol) in one portion. After being stirred 5 min, the mixture was cooled to −78 °C, and ketone **7** (1.01 g,

(20) C. H. Heathcock, M. C. Pirrung, and J. E. Sohn, *J. Org. Chem.*, **44**, 4294 (1979).

(21) We thank Mr. John E. Sohn for this experiment.

5.0 mmol) was added dropwise. This was stirred 2 h, and TMEDA (1.54 mL, 10 mmol) was added followed by (±)-**25** (0.65 g, 5.0 mmol), neat, dropwise. After the mixture was stirred 20 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (5.0 mL) and the mixture allowed to warm to room temperature. The layers were separated, the aqueous phase was extracted with ether (2 × 50 mL), and the combined organic fractions were washed with cold 1% HCl, saturated $NaHCO_3$, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave 857 mg (53%) of product. An analytical sample was prepared by column chromatography on silica gel (E. Merck) with 50% ether in hexanes (R_f 0.50): IR (film) 3460, 2950, 1700, 1370, 1250, 1060, 885, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (9 H, s), 0.90 (9 H, s), 1.35 (3 H, s), 1.40 (3 H, s), 2.5–3.0 (3 H, m), 3.50 (1 H, s), 3.95 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 216.3, 216.2, 215.8, 109.3, 85.9, 85.8, 77.4, 69.2, 69.1, 67.6, 66.9, 66.8, 65.5, 42.3, 35.3, 26.7, 26.6, 26.2, 25.9, 25.8, 25.6, 25.1, 0.6, 0.3. Anal. Calcd for $C_{16}H_{32}O_5Si$: C, 57.80; H, 9.70. Found: C, 58.00; H, 10.02.

(3*S*,6*S*,7*R*)-, (3*R*,6*S*,7*R*)-, (3*R*,6*R*,7*R*)-, and (3*S*,6*R*,7*R*)-6,7-*O*-Isopropylidene-5,6,7-trihydroxy-3-[(trimethylsilyl)oxy]-2,2-dimethylheptan-4-ones (32–35). To a 500-mL, three-necked, round-bottomed flask with a nitrogen inlet, stir bar, and thermometer were added THF (122.5 mL) and diisopropylamine (4.85 mL, 35 mmol). This was cooled to 0 °C, and *n*-butyllithium (22.0 mL of a 1.59 M solution in hexanes, 35 mmol) was added in one portion. After being stirred 5 min, the solution was cooled to −78 °C, ketone **7** (7.00 g, 35 mmol) was added dropwise, and the resulting solution was stirred 2 h. To this was added TMEDA (10.8 mL, 70 mmol) followed by (+)-**25** (4.55 g, 35 mmol), neat, dropwise. After the mixture was stirred 20 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL). This was allowed to warm to room temperature, and the layers were separated. The aqueous phase was extracted with ether (2 × 125 mL), and the combined organic layers were washed with cold 1% HCl, $NaHCO_3$, and brine. This was dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo. The crude product was purified by preparative HPLC with 50% ether in hexanes to give 5.2 g (45%) of a mixture of **32–35**: IR (film) 3460, 2950, 1700, 1370, 1250, 1060, 885, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (9 H, s), 0.90 (9 H, s), 1.35 (3 H, s), 1.40 (3 H, s), 2.5–3.0 (3 H, s), 3.50 (1 H, s), 3.95 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 216.0, 215.8, 214.3, 213.9, 109.4, 86.0, 85.8, 77.6, 69.2, 69.1, 67.6, 67.5, 67.0, 66.9, 65.6, 42.5, 42.3, 35.4, 31.7, 26.8, 26.3, 25.6, 25.5, 25.2, 22.7, 14.2, 0.6, 0.0. Anal. Calcd for $C_{16}H_{32}O_5Si$: C, 57.80; H, 9.70. Found: C, 57.97; H, 9.57.

Conversion of Optically Active 32–35 to 2-Deoxy-D-ribose (36) and 2-Deoxy-D-xylose (37). To a solution of the mixture of aldols **32–35** (490 mg, 1.47 mmol) in CH_2Cl_2 (15 mL) were added dihydropyran (0.16 mL, 1.77 mmol) in CH_2Cl_2 (5 mL) and a small crystal of *p*-toluenesulfonic acid. The mixture was stirred for 12 h at room temperature. The solvent was removed in vacuo and the crude product chromatographed on 50 g of silica gel (E. Merck) with 35% ether in hexanes as the eluant to give 510 mg (83%) of the tetrahydropyranyl ethers: IR (film) 2950, 2840, 1715, 1370, 1255, 1105, 1080, 1030, 890, 840, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.19 (9 H, s), 0.90 (9 H, s), 1.30 (3 H, s), 1.35 (3 H, s), 1.50 (6 H, s), 2.8 (2 H), 3.5 (1 H, m), 4.0 (6 H, br), 4.6 (1 H, m). Anal. Calcd for $C_{21}H_{40}O_6Si$: C, 60.54; H, 9.68. Found: C, 60.88; H, 9.72.

To a solution of lithium aluminum hydride (81 mg, 2.14 mmol) in dry THF (10 mL) under nitrogen was added a solution of the above THP ethers (447 mg, 1.07 mmol) in THF (5 mL), and the mixture was stirred for 2 h at room temperature. The reaction was quenched with H_2O (0.08 mL), 15% NaOH (0.08 mL), and H_2O (0.24 mL) and stirred for an additional 2 h. The mixture was dried ($MgSO_4$), filtered, and concentrated in vacuo to give 358 mg (96%) of analytically pure diols: IR (film) 3450, 2950, 2875, 1380, 1360, 1215, 1140, 1080, 1040, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (9 H, s), 1.25 (3 H, s), 1.30 (3 H, s), 1.60 (6 H, s), 2.80 (2 H, m), 3.80 (10 H, m), 4.60 (1 H, m). Anal. Calcd for $C_{18}H_{34}O_5$: C, 62.40; H, 9.89. Found: C, 62.25; H, 9.76.

To a solution of the above diols (0.346 g, 1 mmol) in absolute ethanol (8 mL) was added a solution of $NaIO_4$ (214 mg, 1 mmol) in H_2O (12 mL) containing enough $NaHCO_3$ to raise the pH to 6.1. The mixture was stirred for 1 h at room temperature. The ethanol was removed in vacuo and the aqueous residue extracted with chloroform (2 × 50 mL). The combined chloroform extracts were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo to give 254 mg (98%) of pure aldehydes: IR (film) 2950, 2740, 1715, 1435, 1385, 1365, 1260, 1215, 1160, 1135, 1065, 1035, 900, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (3 H, s), 1.30 (3 H, s), 1.35 (6 H, m), 2.70 (2 H, m), 3.40 (1 H, m), 4.0 (5 H, m), 4.60 (1 H, m), 9.75 (1 H, m). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.59. Found: C, 60.32; H, 8.38.

To a 100-mL, round-bottomed flask were added a mixture of the above aldehydes (2.27 g, 8.8 mmol) and 60% aqueous acetic acid (44 mL), and the solution was allowed to stir at room temperature for 12 h. The solvents were removed in vacuo, and the residue was chromatographed on silica gel (65 g) with 20% methanol in chloroform as the eluant to give 715 mg (61%) of a 2:1 mixture of **36** and **37** whose spectral properties were identical with those previously reported for a 2:1 mixture.[5]

(3*RS*,5*RS*,6*RS*,7*SR*)- and (3*SR*,5*SR*,6*SR*,7*SR*)-7-(Benzyloxy)-5-butyl-2,2-dimethyl-6-hydroxy-3-[(trimethylsilyl)oxy]-4-octanone (42 and 43). To a solution of 0.80 mL (0.57 g, 5.7 mmol) of diisopropylamine in 15 mL THF at −25 °C was added 3.6 mL (5.4 mmol) of a 1.50 M solution of *n*-BuLi in hexane. The solution was cooled to −78 °C, 150 mL (1.31 g, 5.05 mmol) of ketone **9** was added, and the mixture was stirred for 5 h. TMEDA (1.50 mL, 1.16 g, 9.94 mmol) was then added, followed by 0.80 mL (0.83 g, 5.1 mmol) of 2-(benzyloxy)propanal, and the mixture was stirred for 30 min. The reaction was quenched with 10 mL of saturated, aqueous $NaHCO_3$ and taken up in ether. The organic phase was washed with water and brine and dried over $MgSO_4$, and the solvents were evaporated to give 2.35 g of the crude aldol product as a yellow oil. The crude product was purified by HPLC, and elution with 15% ether/hexane gave 1.05 g (49%) of a 10:1 mixture of aldols **42** and **43** as a clear colorless oil.

The mixture of aldols may be separated by preparative TLC, eluting with 15% ether/hexane, to give the minor isomer **43**: ^1H NMR ($CDCl_3$) δ 0.22 (9 H, s), 0.97 (3 H, m), 1.03 (9 H, s), 1.17–1.67 (6 H, m), 1.30 (3 H, d, J = 6), 2.90–4.03 (4 H, m), 3.83 (1 H, s), 4.53 (1 H, d, J = 4), 4.58 (1 H, d, J = 5), 7.28 (5 H, s). For the major isomer **42**: IR (film) 3500, 1710, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.30 (9 H, s), 1.00 (3 H, m), 1.07 (9 H, s), 1.17–1.80 (6 H, m), 1.40 (3 H, d, J = 6), 2.77 (1 H, br s), 3.37–3.93 (3 H, m), 3.80 (1 H, s), 4.37 (1 H, d, J = 11), 4.70 (1 H, d, J = 11), 7.33 (5 H, s). The major isomer gave the following analytical results. Anal. Calcd for $C_{24}H_{42}O_4Si$: C, 68.20; H, 10.02. Found: C, 68.22; H, 9.91.

(2*RS*,3*RS*,4*SR*)- and (2*SR*,3*SR*,4*SR*)-4-(Benzyloxy)-2-butyl-3-hydroxypentanoic Acids (44 and 45). To a solution of 2.28 g (10.0 mmol) of H_5IO_6 in 20 mL of water was added a solution of 1.05 g (2.49 mmol) of the 10:1 mixture of aldols **42** and **43** in 50 mL of methanol, and the resulting solution was allowed to stand for 3 days. The solvents were evaporated, and the residue was taken up in dichloromethane and extracted with saturated, aqueous $NaHCO_3$. The washes were acidified with 10% aqueous HCl and extracted with ether, and the ether extracts were dried over $MgSO_4$. Evaporation of the solvents left 0.510 g (73%) of a 10:1 mixture of acids **44** and **45** as a pale yellow viscous oil: IR (film) 3450, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3 H, m), 1.07–1.87 (6 H, m), 1.20 (3 H, d, J = 6), 2.53 (1 H, m), 3.43 (1 H, dq, J = 5, 6), 3.83 (1 H, dd, J = 5, 6), 4.33 (1 H, d, J = 11), 4.52 (1 H, d, J = 11), 7.23 (5 H, s). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.56; H, 8.68.

(2*RS*,3*RS*,4*SR*)-2-Butyl-3,4-dihydroxypentanoic Acid 1,4-Lactone (Blastmycinolactol, 46). A mixture of 0.50 g (1.82 mmol) of a 10:1 mixture of acids **44** and **45** and 0.260 g of 10% Pd on carbon in 50 mL of methanol with five drops of concentrated HCl was stirred under an atomsphere of hydrogen for 2 h. The reaction mixture was filtered through a pad of Celite and the solvent evaporated. The residue was dissolved in ether and washed through a short pad of silica, and the solvent was evaporated to give 0.308 g (98% crude yield) of the crude product as a pale yellow solid. Recrystallization from hexane–ethyl acetate gave 0.209 g (67%) of (±)-blastmycinolactol (**46**) as white crystals: mp 53–55 °C (lit.[17] mp 49.5–51.0 °C); IR (CCl_4) 3500, 1785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, m), 1.13–1.97 (6 H, m), 1.42 (3 H, d, J = 6), 2.50 (1 H, m), 3.37 (1 H, br s), 3.73 (1 H, m), 4.12 (1 H, dq, J = 6, 7).

(2*RS*,3*RS*,4*SR*)-2-Butyl-4-hydroxy-3-(isovaleryloxy)pentanoic Acid 1,4-Lactone [(±)-Blastmycinone, 47]. A solution

of 0.155 g (0.901 mmol) of blastmycinolactol (**46**) and 0.36 mL (0.34 g, 1.8 mmol) of isovaleric anhydride in 15 mL of pyridine was allowed to stand at room temperature for 5 days. The reaction mixture was poured into 30 mL of water and extracted with ether. The ether extracts were washed with saturated aqueous $CuSO_4$, saturated aqueous $NaHCO_3$, and water and then dried over $MgSO_4$. Evaporation of the solvent left 0.324 g of a yellow oil. The crude acylation product was passed through a column of silica and then subjected to chromatography on a Chromatron, eluting with 25% ether/hexane, to give 0.213 g (92%) of (±)-blastmycinone (**47**) as a clear colorless oil. Spectral data for this material are consistent with those published.

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Registry No. (±)-**7**, 77079-70-0; (±)-**8**, 72507-39-2; (±)-**9**, 77079-71-1; (±)-**10**, 77079-72-2; (±)-**11**, 77079-73-3; (±)-**12**, 77079-74-4; **13a**, 947-91-1; **13b**, 122-78-1; **13c**, 78-84-2; **13d**, 630-19-3; **13e**, 100-52-7; (±)-**14a** (isomer 1), 72523-82-1; (±)-**14a** (isomer 2), 72507-40-5; (±)-**14b** (isomer 1), 72523-83-2; (±)-**14b** (isomer 2), 72507-41-6; (±)-**14c** (isomer 1), 72523-84-3; (±)-**14c** (isomer 2), 72507-42-7; (±)-**14d** (isomer 1), 72523-85-4; (±)-**14d** (isomer 2), 72507-43-8; (±)-**14e** (isomer 1), 72507-44-9; (±)-**14e** (isomer 2), 72523-86-5; (±)-**15a**, 72507-45-0; (±)-**15a** methyl ester, 77079-75-5; (±)-**15b**, 64869-27-8; (±)-**15c**, 64869-26-7; (±)-**15d**, 72507-46-1; (±)-**15e**, 64869-25-6; (±)-**16**, 77079-76-6; (±)-**19a**, 77079-77-7; (±)-**19b**, 77079-78-8; (±)-**19b** free diol, 77079-79-9; (±)-**20a**, 77079-80-2; (±)-**20b**, 77079-81-3; (±)-**20b** free diol, 77079-82-4; (±)-**21**, 34713-70-7; (±)-**22**, 77079-83-5; (±)-**23**, 72523-87-6; (±)-**25**, 66183-63-9; (+)-**25**, 15186-48-8; (±)-**26**, 72507-47-2; (±)-**29**, 41954-96-5; (±)-**30**, 77079-84-6; (±)-**31**, 77122-10-2; (±)-**32**, 77079-85-7; (3*S*,6*S*,7*R*)-**32**, 77097-67-7; (3*S*,6*S*,7*R*)-**32** THP ether, 77079-86-8; (±)-**33**, 77079-87-9; (3*R*,6*S*,7*R*)-**33**, 77079-88-0; (3*R*,6*S*,7*R*)-**33** THP ether, 77079-89-1; (±)-**34**, 77079-90-4; (3*R*,6*R*,7*R*)-**34**, 77079-91-5; (3*R*,6*R*,7*R*)-**34** THP ether, 77079-92-6; (±)-**35**, 77079-93-7; (3*S*,6*R*,7*R*)-**35**, 77079-94-8; (3*S*,6*R*,7*R*)-**35** THP ether, 77079-95-9; **36**, 533-67-5; **37**, 5284-18-4; (±)-**42**, 77079-96-0; (±)-**43**, 77122-11-3; (±)-**44**, 77079-97-1; (±)-**45**, 77079-98-2; (±)-**46**, 53402-76-9; (±)-**47**, 31203-09-5; ethyl vinyl ether, 109-92-2; pivaldehyde, 630-19-3; 5-methyl-4-hexen-3-one, 13905-10-7; propionyl chloride, 79-03-8; isobutylene, 115-11-7; (*E*)-1-methoxypropene, 4188-69-6; (*Z*)-1-methoxypropene, 4188-68-5; 2-pentyl-1,3-dithiane, 21777-32-2; 2-(2,2-dimethyl-1-hydroxypropyl)-2-pentyl-1,3-dithiane, 77079-99-3; sorbitol, 50-70-4; 1,2:5,6-diacetonide sorbitol, 53735-98-1; methyl (±)-2-(benzyloxy)propionate, 41921-90-8.

Synthesis and Absolute Configuration of Optically Active D_3-Tritwistane, the Gyrochiral Prototype of "Twist" Diamond

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A modification of Barborak's trishomocubane synthesis, when applied to the higher homologue, afforded 8,12-diacetoxy-C_2-bismethanotwistane (**21**) which was converted into (±)-4-C_2-methanoditwistanone (**29**) by a sequence of conversions involving diazomethane ring expansion of the intermediate keto acetates **24** and **25**. Incubation of the resulting C_2-ketone **29** with *Rhodotorula rubra* yielded a mixture of the (−)-C_2-ketone **29** and the (+)-C_2-alcohol **28** with respective 15% and 33% optical purities. Our proposed microbial C_2-ketone rule coupled with CD analysis assigned the 3*S*,5*S* configuration to the (−)-C_2-ketone **29** whose Wolff–Kishner reduction gave (−)-C_2-methanoditwistane (**9**). Demjanov rearrangement of the amine **31** prepared from the (−)-C_2-ketone **29** followed by removal of the functional group provided (−)-D_3-tritwistane (**10**) ($[M]_{D,abs}$ −1067°), the prototype of "twist" diamond, which was found to be converted into diamantane (congressane, **42**) by aluminum bromide treatment.

Our continuing interests in gyrochiral molecules with twisted π-electron systems have resulted in our reporting the first successful syntheses of [*n*][*m*]paracyclophanes,[1] a series of [*n*]chochins,[2] an anti-Bredt-rule compound,[3] and trans doubly bridged ethylenes[4] all in optically active modifications with known absolute configurations, while our another interests in gyrochiral[5] cage-shaped molecules have led us to expend our efforts to prepare the interesting class of compounds[6] illustrated in Figure 1.

A topological characteristic common to the cage-shaped hydrocarbons **2**–**15** is the D_3-twisted bicyclo[2.2.2]octane moiety (shown with dotting) whose conceptual diagonal bridging with single bond, methano and ethano groups should generate all these compounds with rigid conformation. Since cubane (**16**, O_h symmetry) can be regarded to be composed of two enantiomeric D_3-bicyclo[2.2.2]octane molecular frameworks fused together, the pentacyclic molecules **7**–**15** can also be envisaged to be derived by its dissymmetric homologation with methano and/or ethano bridges.

Reflecting these stereochemistries, these cage-shaped hydrocarbons are chiral except for homocubane (**14**) and basketane (**15**) both belonging to the C_{2v} point group. Among the remaining 12, with exceptions of asymmetric C_1-methanotwistane (**5**) and C_1-homobasketane (**12**), 10 are gyrochiral, belonging to either the C_2, D_2, or D_3 point group.

Little imagination would be required to realize that these rigid cage-shaped compounds with well-defined conformations and symmetries should provide ideal substrates for exploring the stereochemistry around the active sites of redox enzymes, and our efforts in this direction have been rewarded in our finding of the microbial[7] and horse

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