Acyclic Stereoselection. 7. Stereoselective Synthesis of 2-Alkyl-3-hydroxy Carbonyl Compounds by Aldol Condensation[1,2]

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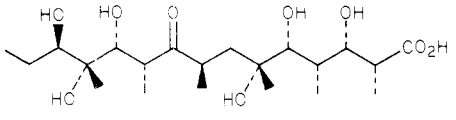
The stereochemistry of the aldol condensation of preformed lithium enolates of a variety of ethyl ketones and propionic acid derivatives with aldehydes has been investigated. It is found that certain compounds give completely or nearly completely one diastereomeric enolate and that the stereostructure of the resulting aldol is correlated with the stereostructure of the enolate from which it is formed. The observed stereochemistry may be understood in terms of an ordered transition state in which both oxygens are oriented in more or less the same direction. It is shown that the observed stereochemistry is kinetically controlled. In many cases, the initial aldol adduct equilibrates to furnish predominantly a threo isomer. The rate of equilibration varies widely, ranging from very fast at -60 °C with the propiophenone-benzaldehyde adduct to slow at 25 °C for the ethyl *tert*-butyl ketone-benzaldehyde adduct. The equilibration behavior of lithium ketolates is compared with that of the zinc ketolates, and some differences are noted. A method for achieving erythro-threo equilibration via a chloral hemiacetal is presented. A new reagent is introduced (trimethylsilyloxy ketone **36**) which may be used to stereoselectively homologate an aldehyde to an erythro α-methyl-β-hydroxy acid. As an application of the use of stereoselective aldol condensations in synthesis, (±)-ephedrine (**48**) has been synthesized from benzaldehyde in 71% overall yield.

Introduction

When planning and executing the synthesis of a complex organic compound, the chemist must cope with three distinct and interrelated problems: elaboration of the requisite molecular framework, placement of the necessary functional groups at their proper sites, and control of relative chirality at the various points of asymmetry in the desired product. Of these three problems, effective control of stereochemistry is often the most vexing, particularly when the elements of asymmetry do not reside in a small ring. The macrolide antibiotics[3] provide cogent examples of synthetic problems which are dominated by considerations of reaction stereoselectivity. Consider erythronolide A seco-acid (**1**). This substance is no more than a



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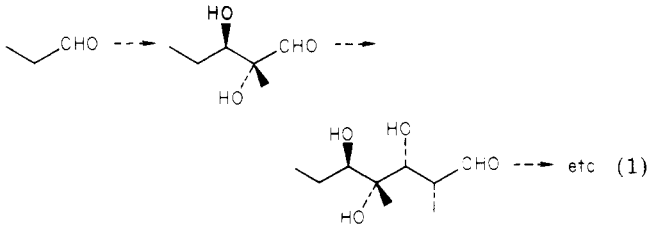
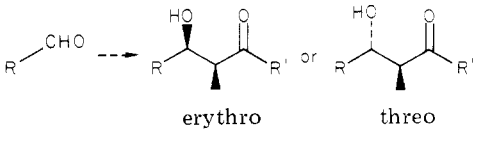
branched-chain carboxylic acid bearing a number of simple functional groups, and it is not difficult to conceive of a sequence of reactions which will lead to it. Even so, compound **1** and its relatives present formidable synthetic challenges because of their many centers of asymmetry.[4]

Compounds such as **1** might be available by a series of aldol condensations, as shown schematically in eq 1. Each



(1)

arrow in the equation represents one or more steps in which the overall result is addition of the elements of 2-hydroxypropanal, propanal, etc. In order for such an aldol extension approach to be viable, one must be able to achieve high stereoselectivity in the individual condensations. There are two types of stereoselectivity which must be considered in the context of such a plan. As illustrated by eq 2, each condensation results in the cre-



erythro threo (2)

ation of *two* new centers of asymmetry, which can have either the erythro or threo relative configuration.[5] Furthermore, all but the first condensation of such an approach would involve addition of a reagent to a *chiral* substrate; attack can occur at either diastereotopic face of the substrate, leading to *four* diastereomeric products (eq 3). In any addition to an α-chiral carbonyl compound, the major diastereomer may be predicted by application of Cram's empirical rules for asymmetric induction.[6] For

(1) For paper 6, see C. H. Heathcock, M. C. Pirrung, C. T. Buse, J. P. Hagen, S. D. Young, and J. E. Sohn, *J. Am. Chem. Soc.*, submitted for publication.

(2) Portions of this work have been reported in preliminary form: (a) C. T. Buse, W. A. Kleschick, and C. H. Heathcock, 172nd National Meeting of the American Chemical Society, San Francisco, CA, Aug 30, 1976 (Abstract ORGN-041); (b) W. A. Kleschick, C. T. Buse, and C. H. Heathcock, *J. Am. Chem. Soc.*, **99**, 247 (1977); (c) C. T. Buse and C. H. Heathcock, *ibid.*, **99**, 8109 (1977); (d) C. H. Heathcock, 14th Euochem Conference on Stereochemistry, Burgenstock, Switzerland, May 1, 1978; (e) 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.

(3) (a) W. D. Celmer, *Pure Appl. Chem.*, **28**, 413 (1971); (b) W. Keller-Schierlein, *Fortschr. Chem. Org. Naturst.*, **30**, 313 (1973).

(4) For syntheses of the macrolide antibiotics methymycin and erythromycin B, see (a) S. Masamune, H. Yamamoto, S. Kamata, and A. Fukuzawa, *J. Am. Chem. Soc.*, **97**, 3513 (1975); (b) E. J. Corey, S. Kom, S. Yoo, K. C. Nicolaou, L. S. Melvin, Jr., D. J. Brunelle, J. R. Falck, E. J. Trybulski, R. Lett, and P. W. Sheldrake, *ibid.*, **100**, 4620 (1978).

(5) It has been convenient for us to have a stereostructural nomenclature which is invariant of the nature of R and R' (eq 2). 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 β-hydroxy substituent both extend toward the viewer or away from the viewer, this is the erythro diastereomer.

(6) (a) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828, 5851 (1952). (b) D. J. Cram and K. R. Kopecky, *ibid.*, **81**, 2737 (1959). (c) When we refer to "Cram's rule addition" to a chiral, α-hydroxy aldehyde, we mean the major isomer which would result from application of Cram's cyclic model.[6b]

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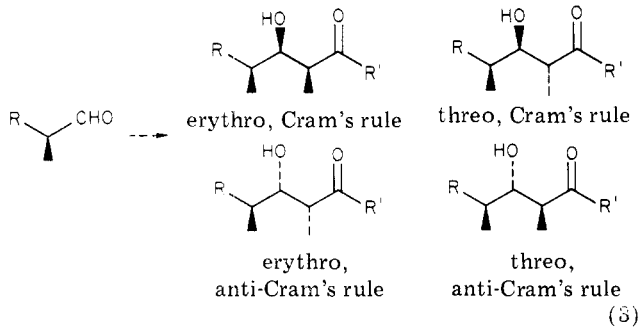


(3)

purposes of nomenclature, we shall refer to the four possible diastereomeric products from a condensation of the type depicted in eq 3 as the erythro, Cram's rule; threo, Cram's rule; erythro, anti-Cram's rule; and threo, anti-Cram's rule products, respectively.

Analysis of the aglycon seco acids of a number of the macrolide antibiotics reveals that the stereoselectivity necessary for most of the hypothetical condensations in an aldol extension approach is that characterized as erythro, Cram's rule. For example, in erythronolide A seco-acid (1), the first condensation must be erythro, the second erythro, Cram's rule,[6c] the third either threo, Cram's rule or erythro, anti-Cram's rule, the fourth either erythro, Cram's rule or threo, anti-Cram's rule, and the fifth and sixth both erythro, Cram's rule[6c] (since C_7 and C_9 in compound 1 are not centers of asymmetry, there are two modes of stereoselection each for the third and fourth condensations which would suffice; in the first case the β-hydroxyl is destined to become a carbonyl and in the second it is destined to be removed). We have initiated a research program to devise methods for control of the stereochemical outcome of aldol condensations for eventual application in such an approach to the synthesis of macrolides. In this paper, we report results of our initial investigations on stereoselection in the reaction of preformed enolates of ketones, esters, and amides to simple aldehydes, as well as an exploitation of these initial results for the highly stereoselective synthesis of erythro β-hydroxy acids.

Results

We began our investigations by surveying the condensation of a number of preformed lithium enolates of ethyl ketones and propionic acid derivatives with benzaldehyde. The general procedure is outlined in Scheme I. The enolate composition was determined by treating the enolate mixture with chlorotrimethylsilane and analyzing the resulting mixture of enol ethers by nuclear magnetic resonance spectroscopy. Aldol stereoselectivity was determined by allowing the enolate solution to react with benzaldehyde at −72 °C for 10 s. The crude aldol product was analyzed by ^1H NMR[7] or ^{13}C NMR.[8] Data are summarized in Table I.

The only method which has heretofore been effective for the assignment of stereostructure to trisubstituted enol ethers is ^1H NMR. House and co-workers have pointed out that the vinyl proton in an *E* diastereomer, **6**, generally resonates downfield of the corresponding proton in the *Z* diastereomer **5**. However, this method is not always applicable. For example, the appropriate resonances in the

Table I. Reaction of Preformed Lithium Enolates of Compounds 2 with Benzaldehyde (Scheme I)

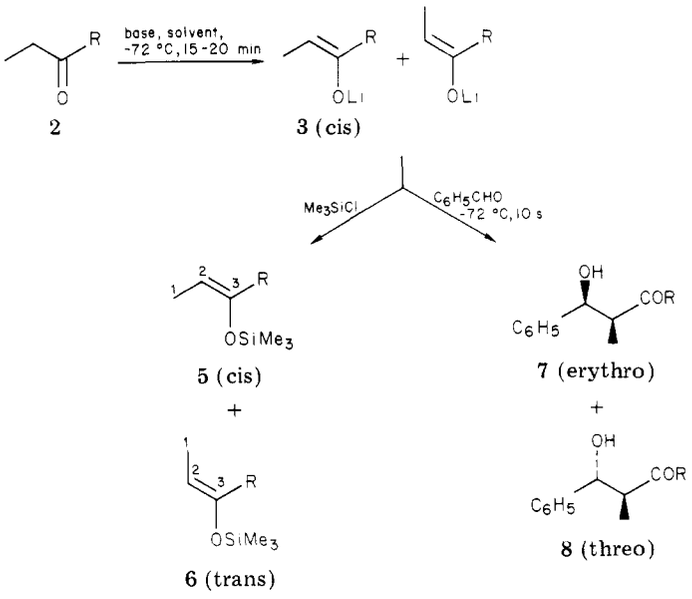
entry	R	base[a,b]	cis/trans[c] (3/4 = 5/6)	erythro/threo (7/8)
1	LiO	LDA		45:55
2	CH_3O	LDA	5:95	62:38
3	$CH_3OCH_2CH_2OCH_2O$	LDA	*d*	23:77
4	*t*-C_4H_9O	LDA	5:95	49:51
5	*t*-C_4H_9O	LTMP	*d*	35:65
6	(*i*-$C_3H_7)_2N$	LDA	81:19	63:37
7	(*i*-$C_3H_7)_2N$	LTMP	52:48	68:32
8	H	*e*	100:0	50:50
9	H	*e*	0:100	65:35
10	C_2H_5	LDA	30:70	64:36
11	C_2H_5	LCPA	35:65	62:38
12	C_2H_5	LHMDS	66:34	77:23
13	C_2H_5	LTMP	20:80	66:34
14	*i*-C_3H_7	LDA	60:40[h]	82:18
15	*i*-C_3H_7	LCPA	59:41[h]	75:25
16	*i*-C_3H_7	LHMDS	>98:2	90:10
17	*i*-C_3H_7	LTMP	32:68	58:42
18	*i*-C_3H_7	*e*	0:100	45:55
19	*t*-C_4H_9	LDA	>98:2	>98:2
20	*t*-C_4H_9	LHMDS	>98:2	>98:2
21	1-adamantyl	LDA	>98:2	>98:2
22	$(CH_3)_3Si$	LDA	38:62	58:42
23	C_6H_5	LDA	>98:2	88:12
24	C_6H_5	LCPA	>98:2	87:13
25	C_6H_5	LHMDS	>98:2	88:12
26	C_6H_5	LTMP	>98:2	83:17
27	2,4,6-$(CH_3)_3C_6H_2$	LDA[f]	8:92	8:92
28	2,4,6-$(CH_3)_3C_6H_2$	LDA	5:95	8:92
29	2,4,6-$(CH_3)_3C_6H_2$	LCPA[g]	4:96	9:91
30	2,4,6-$(CH_3)_3C_6H_2$	LHMDS[g]	87:13	88:12
31	2,4,6-$(CH_3)_3C_6H_2$	LTMP[g]	*d*	4:96

[a] Unless otherwise noted, reactions were carried out in THF containing ca. 15% hexane from the *n*-BuLi used to generate the amide base. [b] LDA = lithium diisopropylamide; LCPA = lithium cyclohexylisopropylamide; LHMDS = lithium hexamethyldisilazine; LTMP = lithium 2,2,6,6-tetramethylpiperidide. [c] The prefixes cis and trans refer to CH_3 and OLi. [d] Not determined. [e] Enolate generated by treating the trimethylsilyl enol ether with methyllithium. [f] In ether. [g] Enolate insoluble. [h] About 10% of the tetrasubstituted enolate is formed.

stereoisomeric pairs **5g**–**6g** and **5h**–**6h** differ by only 0.07[10] and 0.06 ppm, respectively (the latter pair constitute an exception to the House generalization).[9c] Furthermore, both stereoisomers must be available in order for this method to be applicable. Assignment of such stereostructures by ^{13}C NMR is straightforward and unambiguous. It is well-established that the allylic carbons in *cis*-alkenes resonate at higher field than those in *trans*-alkenes. The shift is typically 5–6 ppm. For example, the C_4 resonances in *trans*- and *cis*-2-pentenes are 25.8 and 20.3 ppm, respectively.[11] We observe the same effects in stereoisomeric silyl enol ethers. For example, the C_4 (methylene) resonances in **5g** and **6g** occur at 29.4 and 24.0 ppm, respectively. For **5h** and **6h**, the C_4 (methine) resonances are 34.5 and 28.0 ppm. The single silyl enol ether obtained from 2,2-dimethyl-3-pentanone has its C_4 (quaternary) resonance at 36.7 ppm. Since it is known that addition of a methyl group to a methine carbon results in only a small shift,[12] this ether must be the cis isomer **5i**.[13]

(7) M. Stiles, R. Winkler, Y. Chang, and L. Traynor, *J. Am. Chem. Soc.*, **86**, 3337 (1964).
(8) C. H. Heathcock, M. C. Pirrung, and J. E. Sohn, *J. Org. Chem.*, submitted for publication.
(9) (a) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963); (b) F. Bohlmann, C. Arndt, and J. Starnick, *Tetrahedron Lett.*, 1605 (1963); (c) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(10) J. E. Dubois and P. Fellmann, *Tetrahedron Lett.*, 1225 (1975).
(11) M. T. W. Hearn, *J. Magn. Reson.*, **22**, 521 (1976).
(12) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972, pp 55–60.

Scheme I



R = a, OH(OLi)
b, CH_3O
c, $CH_3OCH_2CH_2OCH_2O$
d, t-C_4H_9O
e, $(i\text{-}C_3H_7)_2N$
f, H
g, C_2H_5
h, i-C_3H_7
i, t-C_4H_9
j, 1-adamantyl
k, Me_3Si
l, C_6H_5
m, mesityl

Table II. Percent Cis Enolate (3) as a Function of Base (Chart I)

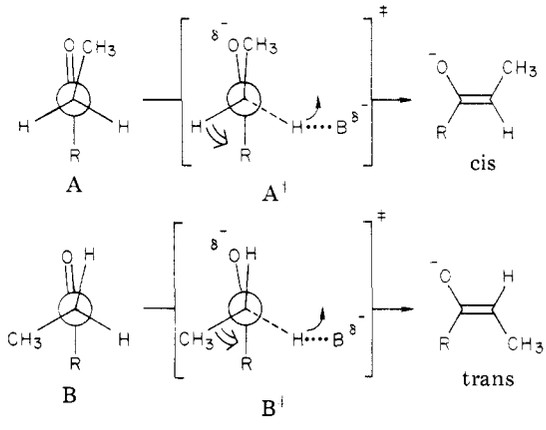
R	LTMP	LDA	LHMDS	[A]/[B] (Scheme I)
CH_3O		5	*a*	13
2,4,6-$(CH_3)_3C_6H_2$	4	8	87	
C_2H_5	16	30	66	51
i-C_3H_7	32	56	100	82
$(i\text{-}C_3H_7)_2N$	52	81	*a*	
C_6H_5	100	100	100	221
t-C_4H_9	100	100	100	>4000

[a] Esters and amides do not react with this base.

The ^{13}C NMR method may even be utilized to confidently distinguish between the two mesityl-substituted ethers **5m** and **6m**; the C_1-ipso resonances are 136.5 and 134.6 ppm, respectively.

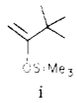
It is clear from Table I that the nature of the amide base used to accomplish deprotonation can have a substantial effect on the cis/trans[14] ratio in the enolates produced. The similar bases lithium diisopropylamide (LDA) and lithium cyclohexylisopropylamide (LCPA) give almost identical cis/trans ratios (entries 10–11, 14–15, 23–24, and 28–29). However, lithium 2,2,6,6-tetramethylpiperidide (LTMP) usually gives more trans enolate than LDA, while lithium hexamethyldisilazine (LHMDS) gives more cis enolate. Data for a series of compounds are collected in Table II. In addition to the effect of base on the cis/trans ratio, Table II also reveals that, with the bases LTMP and LDA, the amount of cis enolate increases as the size of R increases.

Scheme II. Transition States for Formation of cis and trans Enolates



We shall discuss these deprotonation reactions in terms of the diagrams depicted in Scheme II. At the outset of the discussion, we may note that conformer A is more stable than conformer B.[15] The difference in energy of conformers A and B is 800 cal mol^{-1} in propionaldehyde[15] and is presumably greater in ketones and esters, in which R is larger than hydrogen. In fact, the difference between rotomers A and B is just an additional gauche interaction, so we might expect that the relative energies of the two rotomers can be approximated by adding the value for a gauche interaction between methyl and a given group R to the quantity 800 cal mol^{-1}. We can use one-half the conformational free energy difference of an R-substituted cyclohexane as a measure of this gauche interaction for R. For example, the best A value for ethyl is 1750 cal mol^{-1}.[16] From this value, we can estimate that conformer A is 1675

(13) Confirmation for this assignment is obtained by comparing the spectrum of **5i** with that for enol ether i, in which the quaternary resonance occurs at 36.1 ppm. The trans-γ substituent effect in going from i to **5i** is +0.6 ppm, a normal value.



i

(14) We have chosen to refer to the stereoisomeric enolates as cis and trans (CH_3 relative to OLi or $OSiMe_3$) in order that the same description will always refer to the same type of structure, regardless of whether the enolate is derived from a ketone, aldehyde, or ester.

(15) G. J. Karabatsos and N. Hsi, *J. Am. Chem. Soc.*, 87, 2864 (1965).
(16) J. A. Hirsch, *Top. Stereochem.*, 1, 199 (1967).

cal mol^{-1} more stable than B, which corresponds to a ratio of 51 at −70 °C. Estimated conformer ratios at −70 °C for a few compounds are included in Table II (column 5).

We may also make the assumption that, since the low-energy conformations of the ketone are ones in which a bond (C–H or C–C)[15] eclipses the C–O bond and since a bond also eclipses the C–O bond in the product enolate, this geometric relationship obtains throughout the deprotonation process. Thus, the only molecular reorganization we need consider as the C–H bond breaks is the movement of H or CH_3 into coplanarity with the C–R bond (double arrows in Scheme II). That is, the interaction which causes conformer B to be less stable than conformer A will be exacerbated in the transition state for deprotonation.

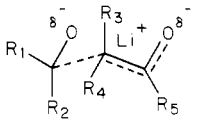
This analysis leads us to anticipate that the cis enolate will be more favored as R becomes larger, regardless of the base used, as is found (Table II). What is not so evident from this analysis is why the trans enolate should be formed at all, especially in light of the realization that the trans enolate is also less stable than the cis.[17] Thus, there must be some factor which raises the energy of transition state A‡ relative to B‡, and this factor must be more important with LTMP than with LDA than with LHMDS. The only reasonable conclusion which may be drawn is that this unknown factor involves a steric interaction between the approaching base and the methyl group in conformation A. In order for the base to interact differently with the methyl in the two conformations, it must *not* approach along the axis of the C–H bond, but rather over the face of the incipient enolate plane. This is reasonable on two grounds. First, this releases Li^+ nearer to the oxygen of the developing enolate. Second, since the developing p orbital at the enolate carbon must eventually overlap with the π system of the carbonyl group, the proton which is being removed must move from its starting position (dihedral angle of 60° to the carbonyl plane) to a position which is roughly perpendicular to the carbonyl plane (single arrows in Scheme II). A similar argument has been advanced to account for the effect of HMPT on the cis/trans ratio in deprotonation of esters by LDA.[18]

The observation that LTMP gives less cis enolate than LDA is consistent with this reasoning.[19] One might have expected LHMDS also to give less cis enolate than LDA, since the trimethylsilyl group is probably larger than an isopropyl group.[20] However, we must also note that this base is considerably less reactive than either LDA or LTMP; in fact, it is not possible to deprotonate propionic acid esters or amides with LHMDS in THF at −70 °C. Application of Hammond's postulate[26] suggests that for LHMDS the transition state is much more developed than for the other amide bases and that the cis/trans ratio is effectively controlled by the relative stability of the developing products in this case.

Table III. Kinetic Stereoselectivity[27] for the Reaction of Various Enolates with Benzaldehyde (Scheme I)

R	cis enolate 3	trans enolate 4
CH_3O		1.5
t-C_4H_9O		1.0
H	1	1.5
C_2H_5	9	1.0
i-C_3H_7	9	1.0
C_6H_5	7	
t-C_4H_9	>50	
1-adamantyl	>50	
2,4,6-$(CH_3)_3C_6H_2$	>50	<0.02

Chart I. Proposed Transition State for the Aldol Condensation



One last point remains to be clarified on the subject of deprotonations. The mesityl group seems to be anomalous when compared to phenyl. However, an examination of the infrared carbonyl stretching frequencies of propiophenone (1695 cm^{-1}) and 2,4,6-trimethylpropiophenone (1720 cm^{-1}) suggests a reason for this apparent anomaly. Clearly the substituents at C_2 and C_6 inhibit the phenyl ring from being coplanar with the carbonyl group. Thus, in transition state B‡, CH_3 interacts with the *edge* of the phenyl ring, but with the *face* of the mesityl ring. The result is that, with respect to transition states A‡ and B‡, the effective sizes of the two aryl groups are C_6H_5 > 2,4,6-$(CH_3)_3C_6H_2$.

It is also clear from Table I that cis and trans enolates do not always demonstrate the same degree of stereoselectivity in their reactions with benzaldehyde. This is particularly apparent with 2-methyl-3-pentanone (entries 16 and 18), where the cis enolate produces a 90:10 erythro/threo mixture of aldols while the trans enolate produces a 45:55 mixture. Kinetic stereoselectivity[27] was also determined for the reaction of several other enolates with benzaldehyde, either directly from the erythro/threo product ratio when the enolate is stereoisomerically homogeneous or by calculation when product ratios were available from reactions involving enolate mixtures of two or more compositions. Results are collected in Table III.

Table III shows an interesting difference in the stereoselectivity observed with cis and trans enolates. The only nonselective cis enolate is the one derived from propionaldehyde. On the other hand, all the trans enolates are somewhat nonselective, with the exception of the one derived from 2,4,6-trimethylpropiophenone. Dubois and Fellmann have previously made the same observation in the reactions of enolates **3g** and **4g** with pivaldehyde.[10] These results are compatible with a six-center transition state Chart I[10] in which there are two important interactions: between R_2 and R_5 and between R_1 and R_4. Thus, when R_5 is very large (t-C_4H_9, 1-adamantyl, mesityl), the cis enolate gives erythro aldol and the trans enolate gives threo aldol, due to the R_2–R_5 interaction. Even with smaller R_5 groups (C_6H_5, i-C_3H_7, C_2H_5) the cis enolates still

(17) Although there is little real data on the relative stability of such cis and trans lithium enolates, it is known that the cis diastereomer is more stable for potassium enolates,[9a] enol acetates,[9a] and enol ethers.[9a,9c]

(18) R. E. Ireland and A. K. Willard, *Tetrahedron Lett.*, 3975 (1975).

(19) See also E. Nakamura, K. Hashimoto, and I. Kuwajima, *Tetrahedron Lett.*, 2079 (1978).

(20) The conformational preference for trimethylsilyl has not been determined. However, A values for trimethylstannyl and trimethylgermyl are 0.94–1.06[21,22] and 2.1 kcal mol^{-1},[23] respectively. The A value for trichlorosilyl, previously reported to be 0.61 kcal mol^{-1},[24] has been found to be in error and is now believed to be greater than 2 kcal mol^{-1}.[25]

(21) F. R. Jensen, T. I. Moder, and C. C. K. Hsu, *J. Am. Chem. Soc.*, in press.

(22) W. Kitching, D. Doddrell, and J. B. Grutzner, *J. Organomet. Chem.*, **107**, C5 (1976).

(23) W. Kitching, H. Olszowy, J. Waugh, and D. Doddrell, *J. Org. Chem.*, **43**, 898 (1978).

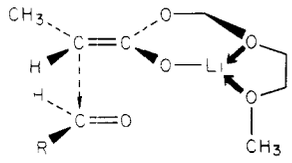
(24) F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Am. Chem. Soc.*, **91**, 344 (1969).

(25) F. R. Jensen, private communication.

(26) G. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

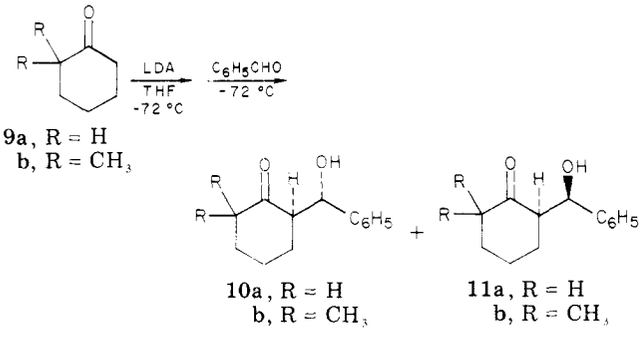
(27) For the purpose of this discussion, we define the kinetic stereoselectivity of a given enolate isomer as the ratio of erythro to threo aldols which are produced from its reaction with a given aldehyde.

Chart II. Possible Transition State for the Aldol Condensation with (2-Methoxyethoxy)methyl Esters



afford mostly the erythro aldol because of the R_2–R_5 interaction. Only when R_5 is hydrogen does the cis enolate become stereorandom. On the other hand, when R_5 is C_2H_5 or i-C_3H_7, the trans enolate gives a 50:50 mixture of erythro and threo diastereomers, presumably as a consequence of the R_1–R_4 interaction, which just balances the R_2–R_5 interaction. When R_5 is smaller (CH_3O and H), the trans enolate actually becomes erythro-selective. It is satisfying that this analysis even explains the curious fact that methyl propionate is more selective than *tert*-butyl propionate, even though both give essentially all trans enolate. This model is also consistent with the observation that the trans enolate **4g** reacts seven to eight times more slowly than the cis enolate **3g**.[10]

Further data pertaining to this point may be found in the reactions of the enolates derived from cyclohexanone and 2,2-dimethylcyclohexanone with benzaldehyde, which give threo and erythro aldols **10** and **11** in ratios of 52:48



9a, R = H
b, R = CH_3

10a, R = H
b, R = CH_3

11a, R = H
b, R = CH_3

and 87:13, respectively. Because ketones **9** are cyclic, they must produce trans enolates. Even though the enolate from **9b** is analogous to that from ethyl *tert*-butyl ketone, it exhibits substantially less stereoselectivity.[28]

It is interesting that the enolate derived from (2-methoxyethoxy)methyl propionate (entry 3, Table I) reacts with benzaldehyde to give predominantly the threo β-hydroxy ester. This behavior has also been observed by Meyers and Reider,[29] who found very high threo selectivity in the reactions of **2c** with aliphatic aldehydes. Meyers and Reider make the intriguing and reasonable hypothesis that the oxygens of the ester alkyl group chelate the lithium of the enolate ion, thus precluding a six-center transition state of the type depicted in Chart I. If such an internally chelated enolate approaches an aldehyde as shown in Chart II (for the trans enolate) such that the H and CH_3 on the enolate double bond are in closest contact with R and H, respectively, on the aldehyde double bond, the threo diastereomer results. In this model, the threo diastereomer is predicted to predominate regardless of enolate geometry. The model also predicts that ester **2c** will show higher selectivity with aldehydes having a fairly bulky alkyl group, as is observed by Meyers and Reider. However, it also predicts that esters of higher acids should show much

(28) Professor Phillip Stotter of the University of Texas, San Antonio, has informed us that he has observed the same type of stereoselectivity with enolates from cyclic ketones.

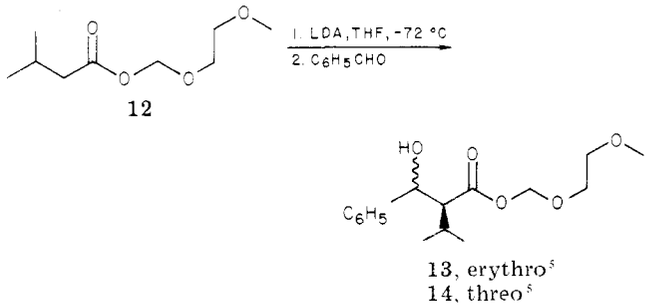
(29) A. I. Meyers and P. Reider, *J. Am. Chem. Soc.*, **101**, 2501 (1979).

Table IV. Reaction of Enol Ether 15 with Benzaldehyde in the Presence of Benzyltrimethylammonium Fluoride

time, h	16/17
0.25	88:12
0.5	86:14
1.0	79:21
2.0	50:50
3.0	19:81
16.0	<5:95[a]

[a] Considerable decomposition at this point.

greater threo selectivity than does the propionate ester. This prediction is not borne out; ester **12** reacts with



12

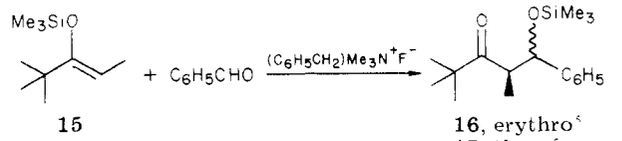
13, erythro[5]
14, threo[5]

benzaldehyde to afford erythro and threo esters **13** and **14** in a ratio of 1:1. A convincing explanation for the behavior of esters such as **2c** must await further experiments.

Several experiments were carried out which were designed to disrupt the nicely ordered transition state depicted in Chart I. In the first of these experiments, we formed the enolate of 2,4,6-trimethylpropiophenone (**2m**) with LDA, then added 4.0 equiv of hexamethylphosphoric triamide (HMPT). After 5 min, partial equilibration of the enolates had occurred to afford a mixture consisting of 66% trans and 34% cis enolates. This enolate mixture reacted with benzaldehyde to give the diastereomeric aldols **8m** and **7m** in a ratio (threo/erythro) of 67:33. A similar experiment using a 42:58 mixture of trans and cis enolates afforded a 40:60 mixture of threo and erythro aldols. Thus, the highly dissociating solvent HMPT does not alter the kinetic stereoselectivity observed with enolates **3m** and **4m**.

We also prepared the potassium enolate from ketone **2m** by allowing the ketone to react with potassium hexamethyldisilazine in THF. A 94:6 ratio of trans and cis enolates **4m** and **3m** results in an 89:11 ratio of aldols **8m** and **7m**. Thus, even with a potassium enolate, the high kinetic stereoselectivity is maintained. The small deviation in this experiment was traced to the fact that the resulting potassium aldol oxides undergo threo–erythro equilibration at a much greater rate than do their lithium counterparts (vide infra).

Finally, we carried out the condensation of benzaldehyde with the cis-trimethylsilyl enol ether **15**, using benzyltrimethylammonium fluoride as catalyst.[30] Initially, the reaction was conducted in THF at room temperature. At various times, aliquots were withdrawn, worked up, and



15

16, erythro[5]
17, threo[5]

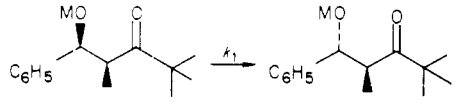
(30) R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **99**, 1265 (1977).

analyzed by ^1H NMR spectroscopy for the erythro/threo ratio of the silylated aldol products **16** and **17**. Data are summarized in Table IV. Utilization of tetra-*n*-butylammonium fluoride under reaction conditions employed by Kuwajima and co-workers[30] led to more reproducible results. When the condensation is conducted at −70 °C for 1 h, the product contains only the erythro silyl ether **16** (97% yield). If the reaction mixture is allowed to warm to room temperature before workup, equilibration occurs (nearly instantaneously) to furnish a 4:1 mixture of **17** and **16**. Thus it appears that even tetraalkylammonium enolates give the same kinetic stereoselectivity as the lithium enolates. Note that these results are contrary to our initial report.[31]

At first sight, the results obtained with lithium enolates in HMPT solution, potassium enolates, and tetraalkylammonium enolates seem difficult to rationalize in terms of the organized transition state hypothesized in Chart I. Certainly a ligand association of the two oxygens with the cation is not necessary, since this is not possible in the tetraalkylammonium case. However, even a Coulombic attraction between these oxygens (both of which bear a fractional negative charge in the transition state) and the cation is probably sufficient to organize the transition state so that both oxygens point more or less in the same direction, as indicated in Chart I. Several groups have examined the aldol condensations of boron enolates and find high stereoselectivity in the sense predicted by a highly organized transition state such as depicted in Chart I, even with ketones and esters not having a bulky group attached to the carbonyl.[32]

At this point, it is necessary to discuss experiments which were carried out in order to demonstrate conclusively that the aldol product ratios we have observed are kinetic, rather than thermodynamic, in nature. Dubois and Fellmann have previously shown that the bromomagnesium salt of erythro aldol **7i** isomerizes almost completely to its threo counterpart **8i** in ether.[33] House and co-workers have argued that the substantial threo selectivity observed in condensations of zinc enolates of various ketones with benzaldehyde results from rapid equilibration of the erythro aldol to the more stable threo aldol, which is stabilized by chelation of the zinc ion.[34]

To gain insight into this point, we examined the equilibration of several erythro/threo pairs (**7**/**8**). The erythro lithium ketolate **18a** was allowed to stand in THF

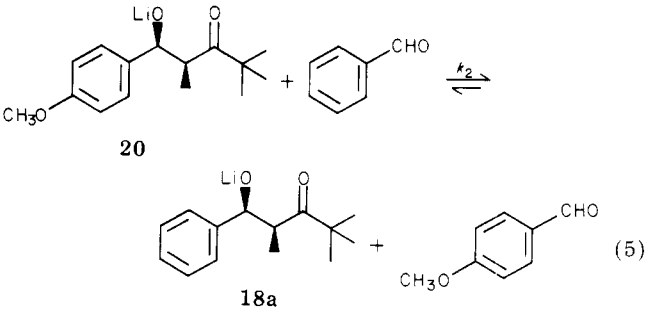


(4)

18 **19**

a, M = Li b, M = $^1/_2$Zn

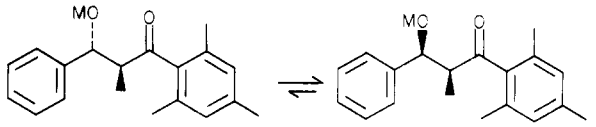
solution at 25 °C, whereupon a very slow equilibration to threo ketolate **19a** occurred ($t_{1/2}^{25°C} \approx 8$ h).[35] On the other hand, if the erythro ketolate **20**, obtained from reaction



20 **18a** (5)

of enolate **3i** with *p*-anisaldehyde, is treated at −70 °C with 1 equiv of benzaldehyde and the resulting solution brought to 0 °C, a fairly rapid equilibration occurs ($t_{1/2}^{0°C} \approx 15$ min) in which erythro ketolate **18a** is essentially the only product. The latter reaction demonstrates that ketolate **18a** is indeed in fairly facile equilibrium with benzaldehyde and enolate **3i**. If we assume that the rate of disappearance of ketolate **20** equals the rate of the reverse aldol condensation, then we may estimate the kinetic stereoselectivity of the reaction of the ethyl *tert*-butyl ketone enolate **3i** with benzaldehyde: it is simply the ratio of the rates of reactions 4 and 5. If we estimate that $t_{1/2}$ for eq 5 at 0 °C is 6 min, the erythro/threo selectivity in the condensation is on the order of 80:1.[36]

Other aldols were observed to undergo erythro/threo equilibration much more rapidly, partly because the corresponding enolates do not show the extraordinary kinetic stereoselectivity displayed by the ethyl *tert*-butyl ketone enolate. The adducts **21a** and **22a**, derived from 2,4,6-



21 **22**

a, M = Li b, M = $^1/_2$Zn

trimethylpropiophenone and benzaldehyde, equilibrate with a half-life in THF at 0 °C of 5 min. The equilibrium composition of the lithium ketolate mixture was found to be 77% erythro (**21**) and 22% threo (**22**). The lithium ketolates derived from aldols **7g**/**8g** and **7h**/**8h** undergo equilibration at rates similar to that observed for lithium ketolates **21a** and **22a**. Although we did not determine accurate rates for pairs **7g**/**8g** and **7h**/**8h**, complete equilibration is achieved within 1.5 h at 0 °C, with both pairs giving an equilibrium ratio of 44% erythro, 56% threo.

Because House et al. have invoked a form of thermodynamic control in aldol condensations involving zinc enolates (vide supra),[34] we compared the equilibration of the lithium and zinc ketolates derived from several aldols (**18** ⇌ **19**, **21** ⇌ **22**, **23** ⇌ **23**). The zinc ketolates were prepared by House's method (adding 0.5 mol of anhydrous $ZnCl_2$ to the lithium enolate before addition of the al-

(31) Our initial report that this experiment gives only threo silylated aldol **17** as the kinetic product (which subsequently equilibrates to erythro aldol **16**[2b]) was incorrect, due to an error in our experimental conditions. In fact, we find that the use of benzyltrimethylammonium fluoride in this reaction leads to fairly unpredictable results. The initial results[2b] were based on *two different* experiments, one of which apparently proceeded very slowly for some reason.

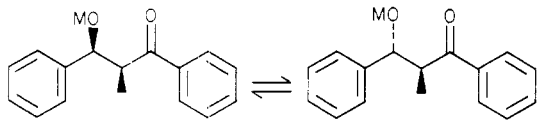
(32) (a) W. Fenzel and R. Koster, *Justus Liebigs Ann. Chem.*, 1322 (1975); (b) S. Masamune, S. Mori, D. Van Horn, and D. W. Brooks, *Tetrahedron Lett.*, 1665 (1979); (c) D. A. Evans, E. Vogel, and J. V. Nelson, *J. Am. Chem. Soc.*, **101**, 6120 (1979).

(33) J. E. Dubois and P. Fellmann, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **274**, 1307 (1972).

(34) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).

(35) Considerable decomposition occurs during the course of this equilibration. Furthermore, it was found that the lithium ketolate of **7i** slowly precipitates from THF solution at room temperature, so the equilibration was conducted in ether. Consequently, the half-life cited is very approximate.

(36) This analysis is clearly approximate, since it is unlikely that the *p*-anisaldehyde adduct undergoes aldol reversion at the same rate as does the benzaldehyde. Nevertheless, the approximation is confirmed by analytical high-pressure LC, which indicates a kinetic ratio of 98.5% **7i** and 1.5% **8i**, and by ^{13}C NMR analysis of a sample of **7i**/**8i** which was prepared using benzaldehyde which was labeled with ^{13}C in its carbonyl group. In the ^{13}C NMR spectrum of the crude product obtained in the latter experiment, the ratio of **7i** to **8i** was found to be 70:1 (work of Dr. J. Hagen).



23 24

a, M = Li b, M = $^1/_2$Zn

dehyde at −10 °C) and also by carrying out the condensation with the lithium enolate and then adding 0.5 mol of $ZnCl_2$. Erythro/threo ratios were determined by high-pressure LC analysis of quenched aliquots. This study revealed some interesting differences in the lithium and zinc systems.

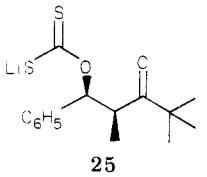
Zinc ketolates **18b** and **19b** equilibrated somewhat more rapidly than did the corresponding lithium ketolates; the half-life for equilibration of **18b** to **19b** is about 3.5 h at 25 °C. This seems to be due largely to a reduced kinetic stereoselectivity of the zinc enolate in the aldol condensation itself. Analysis of the aldol mixture immediately following addition of benzaldehyde to the zinc enolate at −78 °C gives a 92:8 mixture of erythro and threo aldols.

In the system **21** ⇌ **22**, the zinc ketolates undergo equilibration exceedingly rapidly. The half-life for equilibration at −78 °C is on the order of 30 s. It is noteworthy that in this case the position of equilibrium is reversed on changing from the lithium (erythro/threo = 3) to the zinc salt (threo/erythro = 10).

On the other hand, in the system **23** ⇌ **24**, the zinc ketolates equilibrate much more slowly than do their lithium counterparts! The half-life for equilibration of **23b** to **24b** is 4 min at −10 °C and approximately 1 min at −60 °C for equilibration of **23a** to **24a**. In this case also, the cation has an effect on the equilibrium ratio observed, but it is relatively minor (threo/erythro = 3 for zinc and 1.1 for lithium). The rapid equilibration of the lithium ketolates **23a** and **24a** requires very careful temperature control and short reaction times if good kinetic stereoselectivity is to be obtained in condensations of propiophenone. For example, whereas the condensation of **21** with benzaldehyde affords **71** and **81** in a ratio of 88:12 if the reaction is quenched after 10 s at −78 °C, the ratio is only 80:20 after 5 min at this temperature.

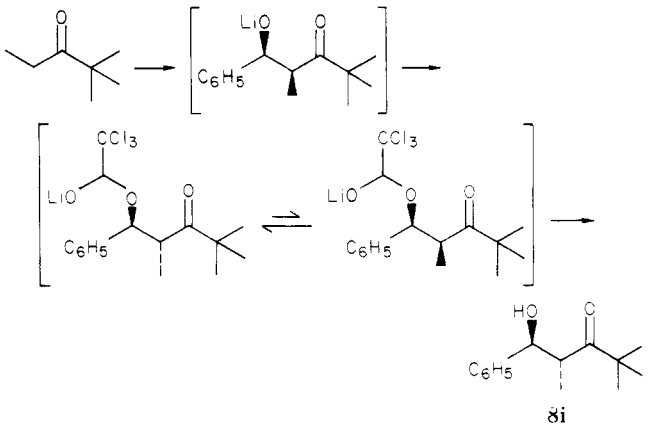
In the process of conducting these equilibration studies, we discovered a method for obtaining the threo aldol **8i**. After adding benzaldehyde to the lithium enolate solution, as usual, one adds 1 equiv of chloral. The resulting mixture is stirred at 0 °C for 5 h and worked up to obtain a hemiacetal which reacts with NaOH in a two-phase mixture (H_2O/ether) to afford threo aldol **8i** of approximately 90% purity (Scheme III). From our foregoing discussion of the slow erythro/threo equilibration of the lithium ketolates **18** and **19** by way of the reverse aldol mechanism, it seems likely that equilibration in the presence of chloral occurs by some other mechanism. We propose that equilibration in this case occurs by intramolecular proton transfer from the position α to the carbonyl group of the alkoxide.

Similar results were obtained by adding 5 equiv of carbon disulfide to the lithium ketolate **18a**. After 8–10 h at 0 °C, the reaction mixture was worked up to afford a 2:1 mixture of threo and erythro aldols **8i** and **7i**. In this case, the equilibration is presumably via the lithium xanthate **25**. Unfortunately, we have not been able to



25

Scheme III



8i

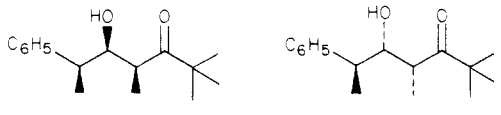
Table V. Condensation of Various Aldehydes with the Lithium Enolate of Ethyl *tert*-Butyl Ketone To Give Erythro Aldols

aldehyde	aldol	% yield	bp, °C (mm)	mp, °C
C_6H_5CHO	7	78	105 (0.3)	55–56
p-$CH_3OC_6H_4CHO$	26	68	146–147 (0.1)	
$C_6H_5CH_2CHO$	27	74	105 (0.1)	
CCl_3CHO	28	83		62–63
n-$C_5H_{11}CHO$	29	66	60–67 (0.1)	
CH_3CH_2CHO	30	81		

generalize these equilibration procedures to other aldols, in part because most other aldols do not equilibrate cleanly to one isomer, as does **7i**.

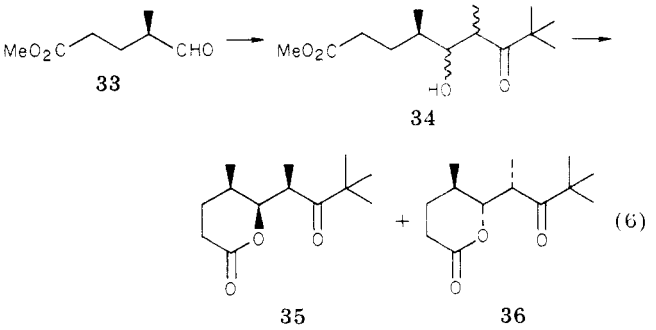
We have also examined the reaction of the highly erythro-selective ethyl *tert*-butyl ketone enolate with several other aldehydes (Table V). In all cases, only the erythro diastereomer was detected.

Finally, we have examined the condensation of ethyl *tert*-butyl ketone with two aldehydes having a center of chirality α to the carbonyl group. Reaction of enolate **3i** with 2-phenylpropanal affords a mixture of two erythro aldols, which are presumed to be the Cram's rule and anti-Cram's rule diastereomers **31** and **32**, in a ratio of 6:1.



31 32

Although these assignments seem secure in light of the general success with which Cram's rule predicts the steric outcome of similar reactions,[37] we performed the condensation on ester aldehyde **33**[38] so that we could directly



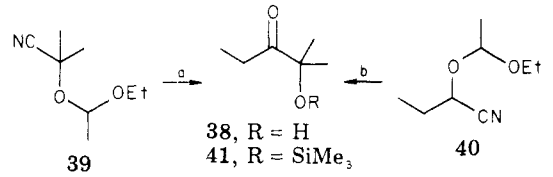
33 34 35 36

(6)

(37) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, NJ, 1971, p 90–93.

(38) G. Stork, A. Brizzolara, H. Landesman, J. Smuskovic, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

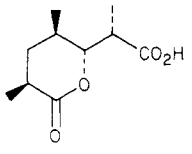
Scheme IV[a]



39 38, R = H; 41, R = $SiMe_3$ 40

[a] a: (1) EtMgBr, THF; (2) H_3O^+, HCl. b: (1) LDA, THF; (2) $(CH_3)_2CO$; (3) H_3O^+; (4) NaOH, H_2O.

determine the stereostructures of the product aldols. The mixture of aldols **34** was hydrolyzed (KOH, CH_3OH) and the resulting hydroxy acids were lactonized (Ac_2O) to obtain two keto lactones (**35** and **36**) in a ratio of 86:14. The ^1H NMR spectra of the separated lactones were compared with the spectrum of the Prelog–Djerassi lactonic acid[39] (**37**). The crucial resonance is the carbinol signal, which

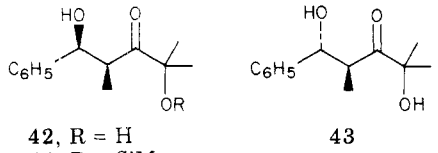


37

appears as a double doublet with coupling constants of 9.5 and 3.8 Hz in lactonic acid **37**. In the major isomer from reaction 6, this resonance appears as a triplet with $J = 6$ Hz; for the minor isomer, it appears as a double doublet with $J = 10$ and 2 Hz.

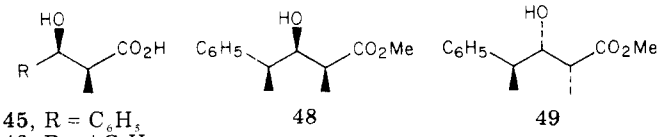
In order to apply this methodology to the stereoselective synthesis of β-hydroxy acids, we developed the reagent **38**, which is available by addition of ethylmagnesium bromide to the protected cyanohydrin of acetone[40] (**39**) or by addition of the protected cyanohydrin of propionaldehyde (**40**) to acetone[41] (Scheme IV).

Since **38** is a hydroxy ketone, it is necessary to use 2 equiv of LDA to convert it into an enolate ion. Addition of the dianion of **38** to benzaldehyde affords aldols **42** and **43** in a ratio of 8:1. Although the erythro product **42** is



42, R = H; 44, R = $SiMe_3$ 43

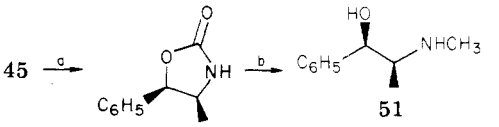
still the major product, the high diastereoselectivity shown by ethyl *tert*-butyl ketone has been lost. However, silyl ether **41**, easily available from **38** by reaction with bis(trimethylsilyl)acetamide, reacts with benzaldehyde to give only the erythro adduct **44**. This substance reacts with periodic acid in methanol to afford the erythro β-hydroxy acid **45** in 77% overall yield. Similar reactions of **41** with



45, R = C_6H_5; 46, R = i-C_3H_7; 47, R = $C_6H_5CH_2$ 48 49

isobutyraldehyde and phenylacetaldehyde afford β-hydroxy acids **46** and **47** in overall yields of 50% and 76%, respectively. Keto ether **41** reacts with 2-phenylpropanal to furnish two diastereomeric adducts. After periodate cleavage and esterification, β-hydroxy esters **48** and **49** are obtained in a ratio of 81:19. The stereostructures of **48** and **49** were established by lithium aluminum hydride reduction to the known crystalline diols.[42]

Scheme V[a]



50 51

[a] a: Et_3N, C_6H_6, $(C_6H_5O)_2PON_3$, Δ. b: $LiAlH_4$, THF, Δ.

To illustrate the utility of stereoselective aldol condensations in natural product synthesis, we have converted the racemic β-hydroxy acid **45** (prepared as outlined above) into (±)-ephedrine (**51**), as depicted in Scheme V. The four-step conversion of benzaldehyde into diastereomerically homogeneous **51** proceeds in 71% overall yield. Reagent **36** has also been utilized in a synthesis of the Prelog–Djerassi lactone, an essential building block in the synthesis of the macrolide antibiotic methymycin.[43]

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. ^1H NMR spectra were determined on the following spectrometers: Varian T-60, Varian EM 390, or Bruker HXS 360 (Stanford Magnetic Resonance Laboratory). ^{13}C NMR spectra were measured at 25.14 MHz with a Nicolet TT-23 spectrometer or at 45.28 MHz on the UCB 180 (a superconducting, 180-MHz, FT instrument). Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Significant ^1H 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 (GLPC) was done with Varian Aerograph A-90P, 920, and 940 gas chromatographs. High-pressure liquid chromatography was performed with a Waters Model ALC/GPC-244 liquid chromatograph (analytical) or a Waters Prep LC/System 500 (preparative). μPorasil columns were used unless otherwise indicated. Elemental analyses were performed by the Microanalytical Laboratory operated by the College of Chemistry, University of California, Berkeley.

(2-Methoxyethoxy)methyl Propionate (2c). A mixture of 7.41 g (100 mmol) of propionic acid, 10.1 g (100 mmol) of triethylamine, and 12.5 g (100 mmol) of (β-methoxyethoxy)methyl chloride[44] in 25 mL of xylene was refluxed for 23 h under nitrogen. The reaction mixture was filtered, dried ($MgSO_4$), and evaporated. The residue was distilled in vacuo through a 15-cm Vigreux column to yield a large forerun and 5.83 g (36%) of clear liquid: bp 66–68 °C (2.5 torr); IR (thin film) 1750 cm^{-1}; ^1H NMR (CCl_4) δ 5.23 (2 H, s), 3.9–3.2 (4 H, unresolved m), 3.32 (3 H, s), 2.32 (2 H, q), 1.12

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(3 H, t); mass spectrum, 117 (2.8, $M^+ - 45$), 89 (51), 87 (26), 59 (100), and 57 (100). An analytical sample was prepared by preparative GLPC (4% FFAP, 10 ft × 0.25 in., 165 °C, retention time 1.3 min).

Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.47; H, 8.77.

2,2-Dimethyl-3-pentanone (2i). To a suspension of 135 g (630 mmol) of pyridinium chlorochromate[45] in 800 mL of methylene chloride was added a solution of 48.8 g (420 mmol) of 2,2-dimethyl-3-pentanol in 80 mL of methylene chloride. The mixture was stirred for 1.5 h, 800 mL of ether was added, and the solution was decanted away from the solid residue. The residue was washed with ether and the combined organic extracts were passed through a pad of Florisil. The solvents were removed at atmospheric pressure through an 18-in. column packed with glass helices. The residue was distilled to give 42.8 g (89%) of a colorless liquid, bp 122–125 °C (lit.[46] bp 125.0–125.8 °C).

1-Propionyladamantane (2j). To a solution of 18.0 g (100 mmol) of 1-adamantanecarboxylic acid in 500 mL of dry ether at 0 °C was added 161 mL of 1.28 M ethyllithium (206 mmol) in benzene/ether over 45 min. The reaction mixture was stirred at room temperature for 38 h and quenched by addition in small portions to a mixture of ice and dilute aqueous HCl. The organic layer was washed with aqueous Na_2CO_3 and water and dried over Na_2SO_4. The solvent was evaporated and the residue was distilled in vacuo through a 15-cm Vigreux column to furnish 16.6 g (87%) of colorless liquid, bp 79–82 °C (0.5 torr). The liquid crystallized on standing to afford a low-melting crystalline solid: mp 31–32 °C; IR (thin film) 1695 cm^{-1}; ^1H NMR (CCl_4) δ 2.42 (2 H, q), 2.02 (~3 H, br m), 1.80 (~12 H, br m), 0.95 (3 H, t); mass spectrum, 192 (6.2, M^+), 135 (100), 93 (17), 79 (9.5).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.31; H, 10.74.

2-Ethyl-2-(trimethylsilyl)-1,3-dithiane. To a solution of 14.8 g (100 mmol) of 2-ethyl-1,3-dithiane in 250 mL of dry THF at −40 °C was added 44.3 mL (105 mmol) of 2.37 M *n*-BuLi in hexane dropwise over 10 min. The reaction mixture was warmed to −20 °C over 1.5 h and stirred at −20 °C for 1 h. To the solution at −20 °C was added 12.7 mL (10.9 g, 100 mmol) of trimethylsilyl chloride (distilled from quinoline under nitrogen immediately prior to use) dropwise, and the reaction mixture was stirred at −20 °C for 4 h. A 25-mL portion of water was added to the reaction mixture, and the THF was evaporated. The residue was diluted with water and extracted three times with ether. The combined ether extracts were washed successively with water, 10% aqueous KOH, and water and then dried (K_2CO_3). The solvent was evaporated and the residue was distilled in vacuo through a 15-cm Vigreux column to give 20.3 g (92%) of colorless liquid: bp 108–109 °C (3.2 torr); IR (thin film) 2994, 1261, 1246 cm^{-1}; ^1H NMR (CCl_4) δ 3.3–2.8 (8 H, unresolved multiplets), 1.07 (3 H, t), 0.20 (9 H, s); mass spectrum 220 (15, M^+), 163 (14), 147 (79), 131 (10), 119 (11), 115 (38), 91 (19), 75 (14), 73 (100).

Anal. Calcd for $C_9H_{20}S_2Si$: C, 49.03; H, 9.14; S, 29.09. Found: C, 48.95; H, 9.16; S, 28.86.

Propionyltrimethylsilane (2k). To a solution of 15.2 g (69 mmol) of 2-ethyl-2-(trimethylsilyl)-1,3-dithiane in 350 mL of 10% water/Me_2SO was added 93.8 g (346 mmol) of $HgCl_2$ and 59.5 g (345 mmol) of $CdCO_3$. The reaction mixture was stirred at room temperature overnight, and volatile components of the reaction mixture (product and water) were distilled at aspirator pressure at temperatures up to 90 °C into a trap maintained at −70 °C. The organic layer in the distillate was separated, dried (K_2CO_3), and distilled in vacuo from K_2CO_3 through a short-path still to furnish 6.60 g (73%) of nearly colorless liquid: bp 82–83 °C (118 torr); IR (thin film) 1640, 1450, 1400, 1365, 1315, 1245, 1095 cm^{-1}; ^1H NMR (CCl_4) δ 2.58 (2 H, q), 0.93 (3 H, t), 0.23 (9 H, s); mass spectrum, 130 (1.3, M^+), 73 (100), 58 (19), 57 (3.8).

Anal. Calcd for $C_6H_{14}OSi$: C, 55.32; H, 10.83. Found: C, 55.44; H, 10.87.

2′,4′,6′-Trimethylpropiophenone (2m). To a solution of 60.1 g (500 mmol) of mesitylene in 200 mL of CS_2 was added 147 g of $AlCl_3$. To the reaction mixture was added 46.3 g (500 mmol) of freshly distilled propionyl chloride dropwise. The reaction mixture began to reflux soon after the commencement of the addition and HCl evolution was observed. The reaction mixture was refluxed for 30 min after the addition was complete, cooled to room temperature, and cautiously added to ice. The CS_2 was allowed to evaporate in a hood overnight, and the residue was extracted with ether. The ether extract was washed with water, 10% aqueous NaOH, and water and dried (Na_2SO_4). Evaporation of the solvent and distillation of the residue through a 15-cm Vigreux column afforded 44.5 g (51%) of nearly colorless liquid: bp 69–72 °C (0.3–0.4 torr) [lit.[47] bp 125 °C (13 torr)]; IR (thin film) 1720 cm^{-1}; ^1H NMR (CCl_4) δ 6.68 (2 H, br s), 2.52 (2 H, q), 2.17 (3 H, s), 1.88 (6 H, s), 1.07 (3 H, t).

The solid material in the pot residue was collected by filtration and recrystallized from ethanol to furnish 8.85 g (7.6%) of white crystalline solid (mp 96.0–98.5 °C) which was identified as 1,3-dipropionyl-2,4,6-trimethylbenzene: IR (nujol mull) 1690 cm^{-1} (br); ^1H NMR (CCl_4) δ 6.78 (1 H, s), 4.25 (4 H, q), 2.12 (6 H, s), 1.95 (3 H, s), 1.12 (3 H, t); mass spectrum 232 (9.4, M^+), 203 (100), 147 (9.5).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.62; H, 8.90.

***N,N*-Diisopropylpropionamide (2e).** Propionyl chloride (8.68 mL, 9.25 g, 0.1 mol) was cautiously added to an ice-cold solution of 28.2 mL (20.1 g, 0.2 mol) of diisopropylamine in 500 mL of ether. The mixture was allowed to warm to room temperature and allowed to stir for 2 h and then filtered and distilled to obtain 15.2 g (97%) of amide **2e**: bp 37–38 °C (0.2 torr); ^1H NMR ($CDCl_3$) δ 1.10 (3 H, t, J = 7), 1.30 (12 H, complex m), 2.35 (2 H, q, J = 7), 3.3–4.3 (2 H, br s); IR (neat) 1645 cm^{-1}. High resolution mass spectrum required for $C_9H_{19}NO$ 157.1466; observed, 157.1463.

General Procedure for the Trapping of Enolates with Silyl Chlorides. To a solution of 556 mg (5.5 mmol) of diisopropylamine in 20 mL of a dry ethereal solvent (THF or ether) at 0 °C was added dropwise 5.5 mmol of a solution of *n*-BuLi in hexane. After 10 min the solution was cooled to −70 °C, and 5 mmol of the ketone or a solution of 5 mmol of the ketone in an appropriate solvent (in cases where a solid ketone was used) was added dropwise over 3 min. After 20 min, 543 mg (5.5 mmol) of chlorotrimethylsilane was added, and the solution was allowed to warm to room temperature over approximately 30 min. When the reaction mixture reached 0–10 °C, a white solid began to precipitate from the reaction mixture. After stirring for ca. 0.5–1.0 h, the reaction mixture was partitioned between pentane and saturated aqueous $NaHCO_3$, and the pentane layer was separated and dried (Na_2SO_4). In cases where the product trimethylsilyl enol ethers were nonvolatile, the solvent was removed by evaporation at reduced pressure; otherwise, the solvent was removed by careful fractional distillation through a 15-cm Vigreux column. A similar procedure was employed to trap the enolates formed with lithium hexamethyldisilylazine (LHMDS), lithium 2,2,6,6-tetramethylpiperidide (LTMP), and lithium cyclohexylisopropylamide (LCPA); in each case 5.5 mmol of the appropriate amine was used. For LHMDS, it was necessary that the reaction run for 1 h in order to assure complete deprotonation with ketones **2g**, **2h**, **2i**, and **2l**, and for 2 h with ketone **2m**.

The lithium enolates of ester **2d** and amide **2e** were prepared and trapped with *tert*-butyldimethylchlorosilane following a procedure described by Ireland and co-workers.[48] Ethers were obtained in quantitative yield.

The ^{13}C and/or ^1H NMR spectra of the crude products were recorded and the ratios of stereoisomeric enol ethers were determined by integration of the characteristic quartets for the vinyl proton resonances (^1H NMR) or by comparison of peak heights for several comparable resonances. Because of their sensitivity to moisture, no attempt was made to characterize these compounds by combustion analysis. Characteristic NMR resonances are collected in Table VI. Cis/trans ratios are collected in Table I.

(*Z*)- and (*E*)-3-[(Trimethylsilyl)oxy]-4-methyl-2-pentene (5h and 6h). To a solution of 11 mmol of LDA in 25 mL of THF

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Table VI. NMR Resonances for Enol Ethers 5 and 6

compd	^{1}H NMR[a] vinyl proton, δ	^{13}C NMR[b] CH_3	vinyl carbons		other[c]
5d	3.92				
5e	4.05				
6e	4.38				
5g	4.45	11.6	100.7	d	29.4
6g	4.57	11.4	100.1	d	24.0
5h	4.47	10.8	99.0	156.8	34.5
6h	4.38	11.2	97.9	156.5	28.1
5i	4.40	11.5	97.3	159.3	36.7
5j	4.45				
5k	5.03				
5k	5.25				
5l	5.12	11.6	105.2	149.0	138.2
6l	5.15				
5m	4.62	10.6	107.3	147.2	ca. 136.5[e]
6m	5.07	12.0	103.0	149.1	134.7

[a] 10% solutions in CCl_4; in each case the cited resonance is a quartet with J = 6.5–7.5 Hz. [b] Approximately 25% solutions in $CDCl_3$; resonances are cited in ppm downfield from internal Me_4Si. [c] In each case, this resonance is for the carbon directly bound to the oxygen-bearing vinyl carbon. [d] Resonance not observed. [e] Partially obscured by another resonance.

at −70 °C (prepared as described for the preceding experiment) was added 1.00 g (10 mmol) of 2-methyl-3-pentanone at such a rate as to maintain the internal temperature below −65 °C. After addition was complete, the solution was stirred for 30 min at −70 °C and 1.195 g (11 mmol) of chlorotrimethylsilane was added. The mixture was allowed to warm to room temperature and then quenched by the addition of 10 mL of saturated aqueous $NaHCO_3$. The resulting mixture was poured into 20 mL of pentane. The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to furnish 1.518 g (88%) of a clear, pale-yellow liquid. The ^{1}H NMR spectrum of this material indicated it to be principally a 3:2 mixture of Z and E ethers **5h** and **6h**, contaminated with a small amount of the tetrasubstituted enol ether. The E and Z stereoisomers were separated by high-pressure LC using hexane as eluant. The Z stereoisomer **5h** eluted first (2.6 column volumes), followed by the E stereoisomer **6h** (3.0 column volumes). The ^{13}C NMR spectra of the high-pressure LC fractions showed them to be pure. ^{13}C NMR ($CDCl_3$), **5h**: δ 0.7, 10.8, 20.7, 34.5, 99.0, 156.8; **6h**: δ 0.4, 11.2, 19.7, 28.1, 97.9, 156.5.

(*Z*)- and (*E*)-1-[(Trimethylsilyl)oxy]propene (5f and 6f). A mixture of 14.5 g (250 mmol) of propanal, 32.6 g (300 mmol) of chlorotrimethylsilane, 84 mL (61 g, 0.6 mol) of triethylamine, and 100 mL of DMF was heated at reflux for 4 h. After cooling to room temperature, 200 mL of pentane was added. The layers were separated and the pentane layer was washed with cold saturated aqueous $NaHCO_3$ (3 × 300 mL) and then rapidly with cold 1.5 M HCl and cold saturated aqueous $NaHCO_3$. After the organic layer was dried (K_2CO_3), the pentane was evaporated and the residue was distilled to give 24.4 g (75%) of a colorless liquid (bp 95–103 °C) which is a mixture of the E and Z isomers (ratio, ca. 3:2). A pure sample of the lower-boiling Z isomer **5f** was obtained by distillation of the mixture through a spinning-band column: bp 96–97 °C; ^{1}H NMR (CCl_4) δ 6.00 (1 H, dq, J = 2, 6), 4.38 (1 H, dq, J = 6, 7), 1.44 (3 H, dq, J = 2, 7), 0.13 (9 H, s). A higher-boiling fraction contained predominantly (90%) the E isomer **6f**: bp 100–103 °C; ^{1}H NMR (CCl_4) δ 6.05 (1 H, dq, J = 2, 12), 4.82 (1 H, dq, J = 7, 12), 1.48 (3 H, dq, J = 2, 7), 0.13 (9 H, s).

General Procedure for Determining the Kinetic Stereoselectivity in the Aldol Condensation of the Lithium Enolates of Ketones with Benzaldehyde. To a solution of 556 mg (5.5 mmol) of diisopropylamine in ether or THF at 0 °C was added 5 mmol of a solution of n-BuLi in hexane. After 10 min the solution was cooled to −70 °C, and 5 mmol of the ketone or a solution of 5 mmol of the ketone in an appropriate solvent (in cases where a solid ketone was used) was added dropwise over 3 min. After addition was complete, the mixture was stirred at −70 °C for an appropriate period of time (see procedure for formation of silyl enol ethers). To the rapidly stirring enolate solution at −70 °C was added 531 mg (5 mmol) of benzaldehyde as rapidly as possible by means of a syringe. An increase in the temperature of the reaction mixture of ca. 20–30 °C was observed. After 3–5 s, 5 mL of saturated aqueous NH_4Cl solution was added, and the reaction mixture was warmed to room temperature. The reaction mixture was diluted with water and extracted three times with ether, and the combined ether extracts were dried (Na_2SO_4). Evaporation of the solvent afforded 83–99% yields of crude material.

Table VII. ^{1}H NMR Chemical Shifts for the Carbinol Resonances of Aldols 7 and 8

R	7 (erythro)[a]	8 (threo)[a]
HO	5.10 (3.5)	4.70 (9.0)
CH_3O	5.08 (4.0)	4.75 (8.5)
t-C_4H_9O	4.80 (6.0)	4.60 (8.5)
$(i$-$C_3H_7)_2N$	5.10 (3.0)	4.70 (8.0)
H	5.08 (4.0)	4.65 (8.0)
C_2H_5	4.80 (6.0)	4.58 (9.0)
i-C_3H_7	4.68 (6.5)	4.55 (8.5)
t-C_4H_9	4.75 (5.0)	4.60 (7.0)[b]
1-adamantyl	4.72 (4.0)	4.58 (9.0)[b]
$(CH_3)_3Si$	4.97 (5.0)	4.65 (9.0)
C_6H_5	5.08 (5.0)	4.92 (9.0)
mesityl	5.25 (3.0)	4.88 (9.0)

[a] Data are reported as δ in ppm from Me_4Si, followed by the vicinal coupling constant in Hz. [b] The chemical shift and coupling constants for these resonances were obtained in an experiment during which the diastereomeric ketols were generated under equilibrating conditions.

Diastereomer ratios were determined by ^{1}H NMR, by integration of the characteristic carbinol resonances. In most cases it was necessary to add a drop of formic acid to the $CDCl_3$ solution in order to eliminate coupling of this resonance with the OH proton. The ^{1}H NMR chemical shifts and coupling constants for the carbinol doublets in aldols **7** and **8** are collected in Table VII. ^{13}C NMR spectra have been published elsewhere.[8] Diastereomer ratios are collected in Table I. For the (β-methoxyethoxy)methyl propionate adducts **7c** and **8c**, the NMR spectrum of the mixture of diastereomers was too complex for convenient analysis. In this case, the crude product was hydrolyzed and the resulting mixture of acids **7a** and **8a** was analyzed.

Kinetic stereoselectivities for the pure cis and trans lithium enolates derived from 2-methyl-3-pentanone were determined by generating the enolates from the respective trimethylsilyl enol ethers. The following procedure is illustrative: To 194 mg (1.13 mmol) of (*Z*)-4-methyl-3-[(trimethylsilyl)oxy]-2-pentene (**5h**) in 5 mL of THF was added 0.75 mL of a 1.6 M solution of methyllithium in ether (1.2 mmol). The resulting clear, pale yellow solution was stirred at 25 °C for 1 h and then cooled to −70 °C. Benzaldehyde (120 mg, 1.13 mmol) was added and the reaction was quenched after 10 s by the addition of 3 mL of saturated aqueous NH_4Cl solution. Standard workup furnished 202 mg (87%) of aldol adduct as a yellow oil, shown by ^{1}H NMR to be an 89:11 mixture of the erythro and threo adducts **7h** and **8h**. The same procedure, applied to the (*E*)-silyl enol ether **6h**, gave **7h** and **8h** in a ratio of 55:45.

Essentially the same procedure was employed with the silyl enol ethers **5f** and **6f**. Thus, 2.06 mmol of **6f** was converted into 333 mg of crude product. Bulb-to-bulb distillation of this material [140 °C bath temperature (0.2 torr)] afforded 251 mg (75%) of a colorless oil, shown by ^{1}H NMR to be a 65:35 mixture of erythro and threo isomers **7f** and **8f**: IR (CCl_4) 3600, 3450, 1720, 1450, 700 cm^{-1}; ^{1}H NMR (CCl_4), **7f**: δ 0.90 (3 H, d, J = 7), 2.23–2.70 (1 H, m), 3.77 (1 H, br s), 4.97 (1 H, d, J = 4), 7.17 (5 H, s), 9.70 (1 H, d, J = 2); **8f**: δ 0.72 (3 H, d, J = 7), 2.23–2.70 (1 H, m), 3.77 (1 H, br s), 4.57 (1 H, d, J = 8), 7.17 (5 H, s), 9.75 (1 H, d, J = 2). A similar reaction with the (*Z*)-silyl enol ether **5f** afforded a 1:1 mixture of **7f** and **8f**. Attempts to add the propionaldehyde enolates to pivaldehyde or isobutyraldehyde were unsuccessful. Compounds **7f** and **8f** proved to be exceedingly fragile substances,

decomposing in a matter of hours at room temperature.

Preparative Procedure for Aldol Condensations with Preformed Lithium Enolates. The following procedure for the preparation of *erythro*-5-hydroxy-2,2,4-trimethyl-5-phenylpentan-3-one (**7i**) is illustrative. A solution of lithium diisopropylamide, prepared from 7.05 mL (5.05 g, 50 mmol) of diisopropylamine and 26.3 mL of a 1.9 M solution of *n*-butyllithium (50 mmol) in hexane, in 50 mL of THF was cooled to −70 °C and 5.70 g (50 mmol) of 2,2-dimethylpentan-3-one was slowly dropped in. The solution was stirred at −70 °C for 30 min and then 5.08 mL (5.30 g, 50 mmol) of benzaldehyde was added. After the solution was stirred for 10 min at −70 °C, saturated aqueous NH_4Cl was added and the mixture was allowed to warm to room temperature. The reaction mixture was worked up in the usual manner to provide 8.6 g (78%) of a viscous white oil [bp 105 °C (0.3 torr)] which crystallized in the freezer. Recrystallization from hexane gave white crystals (mp 55–56 °C). The ^1H NMR spectrum of this material is in agreement with that published by Dubois and Fellmann.[49] Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.32; H, 9.12.

In one such run, the lithium ketolate solution was allowed to warm to room temperature instead of being worked up as usual. Samples were withdrawn, quenched, and analyzed by ^1H NMR; after 8 h the remaining aldol was a 1:1 mixture of erythro and threo diastereomers.

The following pure aldols were also prepared by the foregoing general procedure.

***erythro*-1-(1-Adamantyl)-3-hydroxy-2-methyl-3-phenyl-1-propanone (7j)** was obtained in 97% crude yield on a 10.0-mmol scale. Recrystallization from hexane provided 1.96 g (66%) of crystalline solid: mp 101.5–103.5 °C; IR (CCl_4) 3570, 1680 cm^{-1}; ^1H NMR (CCl_4) δ 7.22 (5 H, s), 4.75 (1 H, d, J = 4), 3.38 (1 H, br s), 3.15 (1 H, dq, J = 5, 7), 1.82 (3 H, unresolved m), 1.67 (12 H, unresolved m), 0.97 (3 H, d); mass spectrum, 192 (15, $M^+ - C_6H_5CHO$), 135 (100), 107 (23), 106 (44), 105 (41), 93 (46), 81 (14), 79 (49), 78 (18), 77 (68), 67 (18). Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.42; H, 8.64.

***threo*-3-Hydroxy-3-phenyl-2,2′,4′,6′-tetramethylpropiophenone (8m)** was obtained in quantitative crude yield on a 3.0-mmol scale. After the mixture was allowed to stand at room temperature for 2 days, a large portion of the crude product had crystallized. This material was collected by suction filtration and recrystallized from hexane to yield 441 mg (52%) of white crystalline solid: mp 97–99 °C; IR (CCl_4) 3610, 1685 cm^{-1}; ^1H NMR (CCl_4) δ 7.23 (5 H, s), 6.73 (2 H, s), 4.93 (1 H, d, J = 9), 3.25 (1 H, quintet), 2.21 (9 H, br s), 0.80 (3 H, d); mass spectrum, 262 (1, $M^+ - H_2O$), 176 (12), 147 (100), 119 (33), 106 (26), 105 (25), 91 (18), 77 (41). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.97; H, 7.82.

***N,N*-Diisopropyl-*erythro*-3-hydroxy-2-methyl-3-phenylpropionamide (7e).** Application of the normal procedure on a 5.0-mmol scale provided 1.25 g (95%) of a mixture of hydroxy amides, shown by ^1H NMR to be a 63:37 mixture of erythro and threo diastereomers. When the solution was allowed to stand at room temperature, the erythro diastereomer **7e** crystallized. Three recrystallizations from hexane furnished pure material: mp 111–113 °C; ^1H NMR ($CDCl_3$ + trace of HCO_2H) δ 1.08 (3 H, d, J = 7), 1.10 (3 H, d, J = 7), 1.25 (3 H, d, J = 7), 1.33 (3 H, d, J = 7), 1.36 (3 H, d, J = 7), 2.85 (1 H, dq, J = 4, 7), 3.65 (1 H, septet, J = 7), 3.95 (1 H, septet, J = 7), 5.10 (1 H, d, J = 4), 7.35 (5 H, br s). Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.95; H, 9.57; N, 5.34. Found: C, 72.87; H, 9.46; N, 5.27.

***erythro*-1-Hydroxy-2,4,4-trimethyl-1-*p*-anisylpentan-3-one (26)** was obtained in 68% yield on a 50-mmol scale. The product was isolated as a pale yellow oil: bp 146–147 °C (0.15 torr); ^1H NMR (CCl_4) δ 6.83 (4 H, m), 4.62 (1 H, d, J = 6), 3.68 (3 H, s), 3.07 (1 H, dq, J = 6, 7), 1.06 (3 H, d, J = 7), 0.95 (9 H, s). Redistillation provided the analytical sample [bp 127–128 °C (0.02 torr)]. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.78; H, 8.75.

***erythro*-5-Hydroxy-2,2,4-trimethyl-6-phenylhexan-3-one (27)** was obtained as a pale yellow oil in 74% yield on a 10-mmol scale: ^1H NMR ($CDCl_3$ + trace of HCO_2H) δ 7.25 (5 H, s), 3.95 (1 H, dt, J = 4, 6.8), 3.03 (1 H, dq, J = 4, 6.8), 2.71 (1 H, d, J = 6.8), 2.69 (1 H, d, J = 6.4), 1.14 (3 H, d, J = 6.8), 1.08 (9 H, s). An analytical sample was obtained by distillation [bp 90 °C (bath temperature) (0.3 torr)]. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.62; H, 9.17.

***erythro*-5-Hydroxy-6,6,6-trichloro-2,2,4-trimethylhexan-3-one (28)** was obtained in 83% crude yield on a 5-mmol scale. The oil crystallized upon standing. Recrystallization from hexane/ether furnished white crystals: mp 62–63 °C; ^1H NMR ($CDCl_3$ + trace of HCO_2H) δ 4.53 (1 H, d, J = 4), 3.83 (1 H, dq, J = 4, 7), 1.31 (3 H, d, J = 7), 1.28 (9 H, s). Anal. Calcd for $C_9H_{15}Cl_3O_2$: C, 41.32; H, 5.78. Found: C, 41.31; H, 5.78.

***erythro*-5-Hydroxy-2,2,4-trimethyldecan-3-one (29)**[50] was obtained as a yellow oil on a 10-mmol scale. After the usual workup, distillation gave 1.26 g (66%) of a colorless oil: bp 60–67 °C (0.1 torr); ^1H NMR (CCl_4) δ 3.6–4.0 (1 H, m), 2.71 (1 H, dq, J = 4.5, 7), 1.16 (9 H, s).

***erythro*-2,2,4-Trimethyl-5-hydroxyheptan-3-one (30)** was obtained as a pale yellow oil in 81% yield on a 5-mmol scale. The ^1H NMR spectrum indicated that the compound was more than 95% pure. ^1H NMR (CCl_4) δ 1.18 (9 H, s), 3.04 (1 H, dq, J = 5, 7), 3.58 (1 H, ddd, J = 5, 6, 7). An analytical sample was obtained by GLC. Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.44; H, 11.52.

***erythro*- and *threo*-3-hydroxy-2-methyl-1,3-diphenylpropan-1-ones (7l and 8l)** were obtained as a pale yellow oil in 96% yield on a 10-mmol scale. As mentioned in the text, this particular lithium ketolate is very prone to erythro–threo equilibration. Addition of aldehyde must be performed at such a rate that the internal reaction temperature remains below −70 °C if maximum stereoselectivity (88% erythro) is to be attained. In this particular experiment, the benzaldehyde was added all at once and the internal reaction temperature rose to −68 °C. The reaction was quenched by the addition of 5 mL of saturated aqueous NH_4Cl 5 s after addition was complete. ^1H NMR analysis of the crude product showed a 79:21 ratio of adducts **7l** and **8l**.

The pure erythro aldol **7l** (mp 74–74.5 °C) was separated by preparative high-pressure LC by elution with 3:1 hexane/ether: ^1H NMR (CCl_4) δ 1.12 (3 H, d, J = 8), 3.53 (1 H, dq, J = 3, 8), 5.07 (1 H, d, J = 3), 7.03–7.93 (10 H, m); IR (thin film) 3500, 1670, 1600, 1580 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.92; H, 6.82.

The pure threo isomer **8l** was obtained by preparative high-pressure LC of a 23:77 mixture of **7l** and **8l**, prepared by equilibration in the presence of zinc chloride (vide infra): ^1H NMR (CCl_4) δ 0.90 (3 H, d, J = 8), 3.60 (1 H, quintet, J = 8), 4.72 (1 H, d, J = 8), 6.97–7.97 (10 H, m); IR (thin film) 3450, 1670, 1600, 1580 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.84; H, 6.71.

(2-Methoxy)ethoxymethyl isovalerate (12) was prepared on a 46-mmol scale as outlined above for the propionate ester **2c**. After the usual workup, the crude product was distilled through a 15-cm Vigreux column to obtain 5.53 g (64%) of ester **12**: bp 110–126 °C (18 torr); IR (thin film) 1740 cm^{-1}; ^1H NMR (CCl_4) δ 1.00 (6 H, d, J = 7), 2.22 (2 H, d, J = 2), 3.42 (3 H, s), 3.80 (4 H, m), 5.32 (2 H, s).

Anal. Calcd for $C_9H_8O_4$: C, 56.82; H, 9.54. Found: C, 57.12; H, 9.44.

(2-Methoxy)ethoxymethyl 2-Isopropyl-3-hydroxy-3-phenylpropionate (13 and 14). These diastereomeric esters were obtained in a ratio of 55:45 (96% yield) by the general procedure for preparative aldol condensations outlined above. The diastereomers were separable by column chromatography on silica gel eluting with 1:1 ether/hexane.

Erythro diastereomer (13): R_f 0.40; IR (thin film) 3450, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (3 H, d, J = 7), 1.07 (3 H, d, J = 7), 2.35 (1 H, m), 2.73 (1 H, dd, J = 4, 8.5), 3.32 (3 H, s), 3.38 (4 H, s), 5.00 (2 H, m), 5.03 (2 H, s), 7.00 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 18.0, 21.7, 26.9, 58.7, 69.0, 71.2, 73.0, 88.8, 126.7, 127.1, 128.2, 172.0. Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 65.14; H, 8.19.

Threo diastereomer (14): R_f 0.22; IR (thin film) 3450, 1735

(49) J. E. Dubois and P. Fellmann, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **274**, 1307 (1972).

(50) We thank Mr. Mark Peterson for carrying out this preparation.

cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (3 H, d, J = 7), 1.00 (3 H, d, J = 7), 2.00 (1 H, m), 2.53 (1 H, dd, J = 6, 6), 3.28 (3 H, s), 3.40 (4 H, br s), 4.86 (2 H, m), 5.13 (2 H, s), 7.20 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 19.6, 21.0, 27.8, 58.9, 59.4, 69.2, 71.4, 72.7, 89.3, 126.0, 127.5, 128.4, 173.7. Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.87; H, 8.23.

(*Z*)-2,2-Dimethyl-3-[(trimethylsilyl)oxy]-3-pentene (15). To a solution of 10.8 mL (7.79 g, 77.0 mmol) of diisopropylamine in 70 mL of dry THF at 0 °C was added 47.8 mL (77.0 mmol) of a 1.61 M solution of *n*-BuLi in hexane. After 10 min the solution was cooled to −70 °C and 7.99 g (70.0 mmol) of 2,2-dimethyl-3-pentanone was added over a 3-min period. After 20 min, 9.77 mL (8.37 g, 77.0 mmol) of chlorotrimethylsilane was added, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred overnight and partitioned between pentane and a saturated aqueous $NaHCO_3$ solution. The pentane extract was dried over Na_2SO_4, and the solvent was removed by fractional distillation through a 15-cm Vigreux column. Distillation of the residue through a short-path still afforded 7.07 g (54%) of colorless liquid: bp 163–165 °C; IR (thin film) 1665, 1475, 1315, 1250, 1220 cm^{-1}; ^1H NMR (CCl_4) δ 4.33 (1 H, q), 1.47 (3 H, d), 0.87 (9 H, s), 0.07 (9 H, s); mass spectrum, 186 (22, M^+), 171 (50), 81 (27), 75 (61), 73 (100). Anal. Calcd for $C_{10}H_{22}OSi$: C, 64.45; H, 11.90. Found: C, 64.28; H, 11.68.

Kinetic and Equilibrium Stereoselectivities in the Benzyltrimethylammonium Fluoride Catalyzed Condensation of (*Z*)-3-[(Trimethylsilyl)oxy]-2,2-dimethyl-3-pentene and Benzaldehyde. To a mixture of 15.2 mg (0.09 mmol) of benzyltrimethylammonium fluoride and 3 mL of THF was added 523 mg (2.81 mmol) of (*Z*)-3-[(trimethylsilyl)oxy]-2,2-dimethyl-3-pentene (**15**) and 0.293 mL (306 mg, 2.89 mmol) of benzaldehyde. The mixture was stirred at room temperature and 0.5-mL aliquots were removed at various time intervals. The aliquots were added to 100 mL of hexane and the hexane solution was washed with water and saturated aqueous NaCl, dried ($MgSO_4$), and evaporated. The proportions of each diastereomer were determined from the ^1H NMR spectra, and the results are summarized in Table IV.

In a run similar to the foregoing, no aliquots were withdrawn. Rather, the entire reaction mixture was worked up after 8 h to obtain 55% yield of the threo-silylated aldol adduct **17**: IR (thin film) 1705, 1250 cm^{-1}; ^1H NMR (CCl_4) δ 7.48 (5 H, s), 4.88 (1 H, d, J = 9.5), 3.38 (1 H, dq, J = 7, 9.5), 1.35 (9 H, s), 0.83 (3 H, d, J = 7), 0.03 (9 H, s); mass spectrum, 292 (1, M^+), 179 (86), 75 (40), 73 (100). High-resolution mass spectrum required for $C_{17}H_{28}O_2Si$ 292.1858; observed, 292.1824.

The authentic erythro silylated aldol **16** was prepared by trimethylsilylation of aldol **7i**. To a solution of 531 mg (5.25 mmol) of diisopropylamine in 2 mL of dry THF at 0 °C was added dropwise 2.34 mL (5.25 mmol) of a 2.24 M solution of *n*-BuLi in hexane. After 10 min this solution was added dropwise to a solution of 1.10 g (5.00 mmol) of *erythro*-1-hydroxy-1-phenyl-2,4,4-trimethyl-3-pentanone (**7i**) in 5 mL of dry THF at −70 °C. After 15 min, 570 mg (5.25 mmol) of chlorotrimethylsilane was added, and the solution was warmed to room temperature over 30 min. After stirring for 1 h, the reaction mixture was partitioned between pentane and saturated aqueous $NaHCO_3$ solution. The pentane extract was dried (Na_2SO_4) and evaporated to furnish 1.33 g (91%) of colorless liquid: IR (thin film) 1705, 1250 cm^{-1}; ^1H NMR (CCl_4) δ 7.30 (5 H, s), 4.80 (1 H, d, J = 9.5), 3.25 (1 H, dq, J = 6.5, 9.5), 1.28 (3 H, d, J = 6.5), 0.77 (9 H, s), 0.08 (9 H, s); mass spectrum, 292 (0.1, M^+), 179 (99.5), 75 (31), 73 (100). The sample was shown to be pure by GLC (8% SE-30, 5 ft × 0.25 in., 195 °C, retention time 4.4 min), and an analytical sample was collected.

Anal. Calcd for $C_{17}H_{28}O_2Si$: C, 69.81; H, 9.65. Found: C, 69.80; H, 9.57.

Tetra-*n*-butylammonium Fluoride. Ten milliliters of a 25% solution of tetra-*n*-butylammonium hydroxide in methanol was treated with 7.5 mL of a 2.43 M aqueous HF solution. The solvents were removed under reduced pressure, leaving a solid white residue.

Anal. Calcd for $C_{16}H_{36}NF{\cdot}2.5H_2O$: C, 62.70; H, 13.48; N, 4.57. Found: C, 63.09; H, 13.44; N, 4.56.

Kinetic and Equilibrium Stereoselectivities in the Tetra-*n*-butylammonium Fluoride Catalyzed Condensation of (*Z*)-4,4-Dimethyl-3-[(Trimethylsilyl)oxy]-2-pentene and Benzaldehyde. Tetra-*n*-butylammonium fluoride (89 mg, 0.28 mmol) was heated at 50 °C (0.5 torr) for several hours before it was dissolved in 10 mL of THF. The solution was cooled to −70 °C and a mixture of 653 μL (559 mg, 3 mmol) of (*Z*)-3-[(trimethyl-silyl)oxy]-2,2-dimethyl-3-pentene (**15**) and 335 μL (350 mg, 3.3 mmol) of benzaldehyde was added. The solution was stirred at −70 °C for 1 h, allowed to warm to room temperature, and poured into 300 mL of hexane. The hexane solution was washed with water and saturated aqueous NaCl and evaporated. The residue was taken up in 20 mL of 0.1 N methanolic HCl and after 10 min was poured into 200 mL of 50% ether/hexane. The layers were separated and the organic layer was washed with water and saturated aqueous NaCl, dried ($MgSO_4$), and evaporated to provide 610 mg (92%) of a mixture of hydroxy ketones which was approximately 80% threo as determined from the ^1H NMR spectrum.

In a similar experiment, the reaction mixture was poured into hexane before it was warmed to room temperature. After a similar workup, the yield was 640 mg (97%) of nearly pure erythro hydroxy ketone.

Ketolate–Aldehyde Exchange: Addition of Benzaldehyde to the Ketolate of 5-Hydroxy-2,2,4-trimethyl-5-*p*-anisylpentan-3-one (20 → 18). A solution of lithium diisopropylamide, prepared from 1.41 mL (1.01 g, 10 mmol) of diisopropylamine and 4.2 mL of a 2.4 M solution of *n*-BuLi (10 mmol) in hexane, in 10 mL of THF was cooled to −70 °C and 1.14 g of 2,2-dimethylpentan-3-one was slowly dropped in. The solution was stirred at −70 °C for 20 min and then 1.22 mL (1.37 g, 10 mmol) of *p*-anisylaldehyde was added. After the solution was stirred for 5 min, a 1-mL aliquot was removed and worked up in the usual manner. The reaction mixture was allowed to warm to 0 °C and 1.02 mL (1.06 g, 10 mmol) of benzaldehyde was added. One-milliliter aliquots were removed after 15 and 60 min at 0 °C, worked up, and analyzed by ^1H NMR. After 15 min, the product was a 1:1 mixture of **7i** and **23**. After 60 min, the ratio of **7i** to **23** was 3:7.

Equilibration of *erythro*- and *threo*-3-Hydroxy-3-phenyl-2,2′,4′,6′-tetramethylpropiophenones (7m and 8m). A. Lithium Salts. To a solution of 2.02 g (20.0 mmol) of diisopropylamine in 20 mL of dry THF at 0 °C was added 8.44 mL (20.0 mmol) of 2.37 M *n*-BuLi in hexane dropwise. After 10 min, the solution was cooled to −70 °C, and 3.53 g (20.0 mmol) of 2′,4′,6′-trimethylpropiophenone was added dropwise over 3 min. After 30 min, the solution was warmed to 0 °C and 2.12 g (20.0 mmol) of benzaldehyde was added to the rapidly stirred yellow solution. At various time intervals, aliquots of approximately 1 mL were removed by syringe and added to a saturated aqueous NH_4Cl solution. Each mixture was diluted with water and extracted with ether, and the combined ether extracts were dried over Na_2SO_4. The solvent was removed by evaporation and the ^1H NMR spectrum of each crude product was recorded. The ratios of the diastereomeric ketols were determined by integration of the characteristic doublets for the β-proton of each isomer at δ 5.25 (J = 3 Hz, erythro β-proton) and δ 4.88 (J = 9 Hz, threo β-proton). The results are summarized in Table VIII. Identical results were obtained when this experiment was performed using 1 equiv of *N,N,N′,N′*-tetramethylethylenediamine.

Table VIII. Composition of the Diastereomeric Mixture from the Reaction of the Lithium Enolate of 2′,4′,6′-Trimethylpropiophenone with Benzaldehyde at 0 °C as a Function of Time

time, min	% erythro	% threo
0.3	86	14
0.6	80	20
1.1	72	28
2.1	63	37
3.1	58	42
4.2	51	49
5.2	49	51
10.2	35	65
15.3	29	71
20.3	29	71
25.3	24	76
30.3	23	77

B. Zinc Salts. A solution of lithium hexamethyldisilylazide, prepared from 2.1 mmol each of hexamethyldisilazine and a 1.51 M solution of *n*-BuLi, in 5 mL of ether was cooled to −78 °C. To this solution was added 2.0 mmol of ketone **2m**. After 1 h at −78 °C, 2.1 mmol of benzaldehyde was added, and the solution was stirred for 12 min. At this time, 1.5 mL of 0.69 M $ZnCl_2$ in ether was added all at once. After 1 min, 5 mL of saturated $NaHCO_3$ was added and the reaction mixture was worked up as usual. Analysis of the crude product indicated the presence of 78% threo adduct **8m** and 22% erythro adduct **7m**. Complete equilibration of the zinc salt, which may be achieved by stirring the reaction mixture at −78 °C for 10 min before quenching, provided 91% **8m** and 9% **7m**.

Equilibration of *erythro*- and *threo*-3-Hydroxy-2-methyl-1,3-diphenylpropan-1-ones (7l and 8l). A. Lithium Salts. A solution of lithium diisopropylamide (prepared from 0.30 mL (220 mg, 2.1 mmol) of diisopropylamine and 1.4 mL (2.1 mmol) of a 1.51 M solution of *n*-BuLi in hexane) in 5 mL of ether was cooled to −78 °C and 0.27 mL (270 mg, 2.0 mmol) of propiophenone was added all at once. The solution was stirred at −78 °C for 30 min, after which time 0.21 mL (210 mg, 2.1 mmol) of benzaldehyde was added all at once. After 5 s, 5 mL of a saturated aqueous solution of NH_4Cl was added, and the mixture was allowed to warm to room temperature. The mixture was diluted with 5 mL of ether and washed with water, and the organic layer was dried ($MgSO_4$). Analysis of the product ratios by analytical high-pressure LC (eluting with 4:1 hexane/ether) showed a 82:18 ratio of the erythro and threo adducts.

The reaction was repeated, allowing the mixture to warm to four different temperatures between addition of the benzaldehyde and the quench with the NH_4Cl solution. The following results were obtained when the solution was warmed to the given temperature: −55 °C, after 2:40 min, 59:41 erythro/threo; −35 °C, after 3:55 min, 47:53 erythro/threo; −15 °C, after 6:40 min, 47:53 erythro/threo; 5 °C, after 10:20 min, 47:53 erythro/threo.

B. Zinc Salts. A solution of lithium diisopropylamide (prepared from 0.69 mL (500 mg, 4.9 mmol) of diisopropylamine and 3.3 mL (5.0 mmol) of a 1.51 M solution of *n*-BuLi in hexane) in 8 mL of ether was cooled to −78 °C, and 0.64 mL (650 mg, 4.8 mmol) of propiophenone was added all at once. The solution was stirred at −78 °C for 30 min and then 3.6 mL (2.5 mmol) of a 0.69 M solution of anhydrous $ZnCl_2$ in ether was added. The solution was allowed to warm to −10 °C and was stirred for 20 min, after which time 0.50 mL (520 mg, 4.9 mmol) of benzaldehyde was added. The reaction mixture was stirred at −10 °C, and at fixed time intervals 1-mL aliquots were removed and quenched in saturated aqueous NH_4Cl. These aliquots were diluted with ether and the organic layer dried and analyzed by analytical high-pressure LC as described in A. The results were obtained as follows: 5 s after addition of the benzaldehyde, a ratio of 70:30 erythro/threo was observed; after 15 s, 67:33; after 30 s, 63:37; after 60 s, 59:41; after 2 min, 53:47; after 4 min, 45:55; after 8 min, 33:67; and after 16:30 min, 25:75.

***threo*-1-Hydroxy-1-phenyl-2,4,4-trimethyl-3-pentanone (8i).** To a solution of 5.00 mmol of lithium diisopropylamide in 20 mL of THF at −70 °C was added a solution of 1.10 g of aldol **7i** in 10 mL of THF at such a rate as to maintain the reaction temperature below −65 °C. After addition was complete (a white solid had formed), 737 mg (5.00 mmol) of anhydrous chloral was added and the mixture was stirred while the temperature was raised to 0 °C (the solid dissolved at −10 °C). The resulting solution was stirred for 5 h at 0 °C and then quenched by the addition of 5 mL of saturated NH_4Cl solution. The layers were separated and the organic layer was washed with 20 mL of water and 20 mL of 10% $NaHSO_3$ and dried ($MgSO_4$). Removal of solvent provided 1.72 g of pale yellow oil which was shown by ^1H NMR to be essentially a single compound: ^1H NMR ($CDCl_3$) δ 0.80 (3 H, d, J = 7), 1.23 (9 H, s), 3.2–3.8 (2 H, m), 4.5 (1 H, s), 4.97 (1 H, d, J = 10), 7.37 (5 H, s). A portion of this crude product (1.16 g) was dissolved in 10 mL of ether and stirred vigorously in contact with 10 mL of 5% aqueous NaOH for 5 h at 25 °C. The layers were separated and the organic layer was dried over $MgSO_4$. Removal of solvent furnished 533 mg (72%) of threo aldol **8i** as a pale yellow oil. The analytical sample (mp 65–65.5 °C) was obtained by recrystallization from hexane: ^1H NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 7), 1.07 (9 H, s), 3.08–3.53 (2 H, m), 4.75 (1 H, dd, J = 7, 5), 7.28 (5 H, s). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.37; H, 8.99.

The intermediacy of chloral hemiacetals in the foregoing equilibration was established by the following series of experiments. If the reaction mixture was worked up as soon as the solution consisting of the ketolate of **7i** and chloral had reached 0 °C, there was isolated a substance which had spectral properties consistent with a mixture of stereoisomeric hemiacetals. A sample of this material (75 mg, 0.2 mmol) was dissolved in 5 mL of acetic acid, cooled to 5 °C, and treated with 0.1 mL of an oxidizing solution.[51] Immediate formation of a green solid occurred. After 30 min at 5 °C, 5 mL of water was added and the solution was extracted with ether. The organic extracts were washed with 10% aqueous NaOH and water and dried ($MgSO_4$). Removal of solvent afforded 51 mg of trichloroacetate as a white solid (mp 68–68.5 °C). This substance was identified as the erythro (**7i**) trichloroacetate by comparison of its ^1H NMR spectrum with those of authentic samples of erythro and threo trichloroacetates, prepared as outlined below.

The trichloroacetate of the erythro aldol **7i** was prepared by adding 200 mg of trichloroacetyl chloride (1.1 mmol) to a solution of 220 mg of **7i** (1.0 mmol) in 5 mL of anhydrous pyridine. The resulting solution was stirred at 25 °C for 18 h and then was partitioned between 10 mL of water and 20 mL of ether. The ether layer was washed with 10 mL of water, dried, and evaporated to provide 358 mg (98%) of crystalline trichloroacetate (mp 68–68.5 °C): ^1H NMR ($CDCl_3$) δ 0.80 (9 H, s), 1.32 (3 H, d, J = 6), 3.35–3.95 (1 H, m), 5.90 (1 H, d, J = 10), 7.27 (5 H, s). Anal. Calcd for $C_{16}H_{19}Cl_3O_3$: C, 52.55; H, 5.24. Found: C, 52.56; H, 5.38.

The trichloroacetate of the threo aldol **8i** was prepared in a similar manner (mp 75.5–76 °C): ^1H NMR ($CDCl_3$) δ 0.87 (3 H, d, J = 6), 1.27 (9 H, s), 3.35–3.90 (1 H, m), 5.82 (1 H, d, J = 10), 7.35 (5 H, s). Anal. Calcd for $C_{16}H_{19}Cl_3O_3$: C, 52.55; H, 5.24. Found: C, 52.64; H, 5.28.

The threo aldol **8i** was also prepared in the following manner. To a solution of 1 mmol of lithium diisopropylamide in 10 mL of THF at 0 °C was added 1 mmol of **7i** in 5 mL of THF, followed by 5.0 mmol of carbon disulfide. The clear yellow solution was stirred for 8–10 h at 0 °C, quenched by the addition of saturated NH_4Cl solution, and worked up as usual. The crude product, obtained in quantitative yield, was shown by ^1H NMR to be a 2:1 mixture of threo and erythro aldols **8i** and **7i**.

5-Hydroxy-2,2,4-trimethyl-6-phenylheptan-3-one (31 and 32). A solution of lithium diisopropylamide (prepared from 705 μL (505 mg, 5 mmol) of diisopropylamine and 2.65 mL of a 1.9 M solution of *n*-BuLi (5 mmol) in hexane) in 5 mL of THF was cooled to −70 °C and 565 mg (4.95 mmol) of 2,2-dimethylpentan-3-one was slowly dropped in. The solution was stirred at −70 °C for 15 min and then 650 μL (656 mg, 4.8 mmol) of 2-phenylpropanal was added. After the solution was stirred at −70 °C for 5 min, saturated aqueous NH_4Cl was added and the reaction mixture was worked up in the usual manner to provide 950 mg (80%) of a colorless oil [bp 110 °C (0.35 torr)] which was a mixture of two diastereomers (86:14) as determined from the 360-MHz ^1H NMR spectrum. When the reaction was carried out in the same manner, with the exception that excess acetic anhydride was used instead of saturated aqueous NH_4Cl to quench the reaction, the crude acetoxy ketone was isolated as a white solid in 96% yield. Recrystallization of this material from hexane/ether afforded 1.9 g (65%) of white crystals: mp 70–75 °C; ^1H NMR (CCl_4) δ 7.33 (5 H, s), 5.34 (1 H, dd, J = 3, 10), 3.0 (2 H, m), 2.10 (3 H, s), 1.24 (3 H, d, J = 7), 1.04 (3 H, d, J = 7), 1.00 (9 H, s). An analytical sample was prepared by recrystallization from hexane, mp 76–78 °C. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.03. Found: C, 74.59; H, 8.78.

Methyl 4-Formylpentanoate (33). A solution of 86.4 g (0.69 mol) of *N*-(1-propenyl)piperidine[52] in 550 mL of acetonitrile was cooled to 0 °C and 77.6 mL (74.0 g, 0.86 mol) of methyl acrylate in 200 mL of acetonitrile was added over a period of 20 min. The solution was stirred at room temperature for 16 h and then at reflux for 36 h. After the solution was cooled to room temperature,

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42 mL of acetic acid in 275 mL of water was added and the mixture was refluxed for 8 h. The cooled mixture was treated with solid NaCl to saturate the aqueous layer and the layers were separated. The aqueous layer was extracted with ether and the combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated. Distillation of the residue gave 59.3 g of a colorless liquid: bp 94–96 °C (8 torr); IR (thin film) 2710, 1724, 1712 cm^{-1}; ^1H NMR (CCl_4) δ 9.67 (1 H, d, J = 2), 3.70 (3 H, s), 1.18 (3 H, d, J = 7). No satisfactory analysis could be obtained for this compound. The 2,4-dinitrophenylhydrazone was prepared and recrystallized from ethanol, mp 109.5–111.0 °C. Anal. Calcd for $C_{13}H_{16}N_4O_6$: C, 48.15; H, 4.97; N, 17.28. Found: C, 48.07; H, 5.03; N, 17.18.

7-Oxo-5-hydroxy-4,6,8,8-tetramethylnonanoic Acid δ-Lactone (35 and 36). A solution of lithium diisopropylamide (prepared from 3.52 mL (2.54 g, 25 mmol) of diisopropylamine and 10.4 mL of a 2.4 M solution of n-BuLi (25 mmol) in hexane) in 25 mL of THF was cooled to −70 °C and 2.85 g (25 mmol) of 2,2-dimethyl-3-pentanone was slowly dropped in. After the solution was stirred at −70 °C for 20 min, 3.49 g (24 mmol) of methyl 4-formylpentanoate was added. Saturated aqueous NH_4Cl was added and the mixture was allowed to warm to room temperature. After the usual workup, the crude product was treated with 2 mL of 12.5 M aqueous NaOH in 10 mL of methanol overnight. Water was added and the mixture was extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated. The residue was stirred with excess acetic anhydride at room temperature for 2 h. This solution was evaporated to dryness under reduced pressure to afford 4.75 g (84%) of a thick oil which partially crystallized upon standing. Analysis of the 360-MHz ^1H NMR spectrum of the crude product before crystallization indicated a mixture of two lactones present in a ratio of 86:14. After two recrystallizations from ether/hexane, a sample of the major product was obtained: mp 55–57 °C; ^1H NMR (CCl_4) δ 4.38 (1 H, t, J = 6), 3.40 (1 H, pentet), 1.25 (9 H, s). No satisfactory analysis could be obtained for this compound as it was extremely difficult to recrystallize. The minor isomer was isolated after chromatography of the crude product on silica gel using 10% ether/hexane as the eluant: ^1H NMR (CCl_4) δ 4.46 (1 H, dd, J = 2, 10), 1.25 (9 H, s). The nature of the lactone methine H resonance in the ^1H NMR spectrum of the "Prelog–Djerassi lactone",[39] 4.43 (dd, J = 3.8, 9.5), allows us to make the assignments as shown for **32** and **33**.

2-[(Trimethylsilyl)oxy]-2-methyl-3-pentanone (41). Preparation A. To 42.4 g (0.5 mol) of 2-hydroxybutyronitrile containing one drop of concentrated HCl was added 48 mL (36 g, 0.5 mol) of ethyl vinyl ether at a rate such that the temperature was maintained at ca. 50 °C. After the addition was complete, the mixture was heated at 90 °C for 2 h. Distillation directly from the reaction flask provided 65.7 g (84%) of 2-(1-ethoxyethoxy)-butyronitrile as a mixture of diastereomers, bp 84–96 °C (18 torr).

To a solution of lithium diisopropylamide (prepared from 61.7 mL (44.5 g, 0.44 mol) of diisopropylamine and 293 mL of a 1.5 M solution of n-BuLi (0.44 mol) in hexane) in 200 mL of THF cooled to −70 °C was added dropwise a solution of 65.7 g (0.42 mol) of 2-(1-ethoxyethoxy)butyronitrile in 50 mL of THF. The solution was stirred at −70 °C for 10 min and then 33 mL (26.1 g, 0.45 mol) of acetone was added. The mixture was allowed to warm to room temperature and stir overnight. After the solution was poured into water, the volatile components were removed in vacuo and the residue was extracted with methylene chloride. The combined extracts were dried (Na_2SO_4) and evaporated, and the residue was treated with 100 mL of 10% H_2SO_4 in 200 mL of methanol for 15 min. Most of the methanol was evaporated and the residue was extracted with ether. The ether extracts were shaken with 50 mL of 10 N NaOH for 10 min, dried (Na_2SO_4), and evaporated. Distillation of the residue afforded 31.1 g (64%) of 2-hydroxy-2-methyl-3-pentanone: bp 59–65 °C (18 torr); ^1H NMR (CCl_4) δ 3.78 (1 H, br s), 2.59 (2 H, q, J = 7.5), 1.34 (6 H, s), 1.07 (3 H, t, J = 7.5); IR (thin film) 3455, 1702 cm^{-1}.

A mixture of 31.1 g (270 mmol) of 2-hydroxy-2-methyl-3-pentanone and 27.26 g (134 mmol) of bis(trimethylsilyl)acetamide was heated at 100 °C overnight. After the solution was cooled, the mixture was poured into water and extracted with hexane. The hexane extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue was distilled to provide 40.1 g (79%) of a water-white liquid: bp 69–75 °C (18 torr); ^1H NMR (CCl_4) δ 2.60 (2 H, q, J = 7.5), 1.35 (6 H, s), 1.01 (3 H, t, J = 7.5), 0.18 (9 H, s). Anal. Calcd for $C_9H_{20}O_2Si$: C, 57.35; H, 10.70. Found: C, 57.58; H, 10.68.

Preparation B. To a solution of ethylmagnesium bromide (88.2 mmol) in 200 mL of THF was added 9.36 g of 2-(1-ethoxyethoxy)butyronitrile[40] (59.6 mmol), and the solution was heated at reflux for 40 h. The solution was cooled and 120 mL of a 1:1 solution of methanol and 10% HCl was added. Stirring for 30 min was followed by separation of phases and extraction of the aqueous phase with ether (2 × 200 mL). The combined organic phases were washed with 5% NaOH (2 × 200 mL), 10% HCl (200 mL), and saturated NaCl (200 mL) and dried ($MgSO_4$), and the solvents were removed in vacuo to afford 3.58 g (52%) of essentially pure hydroxy ketone **35**.

***erythro*- and *threo*-2,5-Dihydroxy-2,4-dimethyl-5-phenylpentan-3-ones (42 and 43).** A solution of lithium diisopropylamide (prepared from 2.82 mL (2.02 g, 20 mmol) of diisopropylamine and 13.33 mL of a 1.5 M solution of n-BuLi (20 mmol) in hexane) in 20 mL of THF was cooled to −70 °C and 1.095 g (9.44 mmol) of 2-hydroxy-2-methyl-3-pentanone was slowly dropped in. The solution was warmed to −40 °C and stirred for 1.5 h. After the solution was cooled to −70 °C, 1.02 mL (1.06 g, 10 mmol) of benzaldehyde was added. The solution was stirred at −70 °C for 5 min and then saturated aqueous NH_4Cl was added. The mixture was allowed to warm to room temperature and after the usual workup, 1.95 g (88%) of a viscous pale yellow oil was isolated which partially crystallized on standing. Analysis of the ^1H NMR spectrum of the mixture indicated that it was an approximate 8:1 mixture of diastereomers in which the erythro isomer was assumed to be the major product. A portion (1.73 g) of this material was chromatographed on 100 g of silica gel, with 50% ether/hexane as eluant, to give two fractions. The first fraction (264 mg) crystallized on standing and was recrystallized from ether/hexane to provide white crystals: mp 125–126 °C; ^1H NMR ($CDCl_3$ + trace of HCO_2H) δ 7.37 (5 H, s), 4.66 (1 H, d, J = 9), 3.53 (1 H, dq, J = 7, 9), 1.54 (3 H, s), 1.47 (3 H, s), 0.87 (3 H, d, J = 7). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.12; H, 8.05.

The second fraction slowly crystallized on standing and was recrystallized from ether/hexane to provide white crystals: mp 58–60 °C; ^1H NMR ($CDCl_3$ + trace of HCO_2H) δ 7.32 (5 H, s), 4.89 (1 H, d, J = 6), 3.32 (1 H, dq, J = 6, 7), 1.32 (3 H, s), 1.20 (3 H, d, J = 7), 0.99 (3 H, s). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.98; H, 8.09.

***erythro*-2-[(Trimethylsilyl)oxy]-5-hydroxy-2,4-dimethyl-5-phenylpentan-3-one (44).** Following the general procedure for preparative aldol condensations (see preparation of **7i**), 1.88 g (10 mmol) of keto ether **41** was condensed with 1.06 g (10 mmol) of benzaldehyde. The reaction mixture was quenched by the addition of aqueous NH_4Cl at −70 °C after a reaction time of 1 min. After the normal workup, 2.30 g (78% crude yield) of erythro silylated aldol **44** was obtained as a clear oil. The ^1H NMR spectrum of this material was superimposable with that of the distilled product. Bulb-to-bulb distillation [90 °C (bath temperature) (0.05 torr)] furnished 1.71 g of water-white oil: ^1H NMR (CCl_4) δ 7.25 (5 H, s), 4.87 (1 H, d, J = 4.5), 3.47 (1 H, dq, J = 4.5, 7), 1.22 (3 H, s), 1.13 (3 H, s), 1.04 (3 H, d, J = 7), 0.2 (9 H, s).

***erythro*-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (45).** A solution of 147 mg (0.5 mmol) of the silylated aldol adduct **44** in 10 mL of methanol was treated with 5.2 mL of a 0.54 M solution of H_5IO_6 in water. After 3 h at room temperature, the solvents were removed in vacuo and the residue was extracted with CH_2Cl_2. After the solvent was dried and evaporated, 78 mg (87%) of the erythro β-hydroxy acid **7a** was obtained, identical by ^1H NMR with an authentic sample.

***erythro*-3-Hydroxy-2,4-dimethylpentanoic Acid (46).** A solution of lithium diisopropylamide (prepared from 705 μL (505 mg, 5 mmol) of diisopropylamine and 3.57 mL of a 1.4 M solution of n-BuLi (5 mmol) in hexane) in 5 mL of THF was cooled to −70 °C and 927 mg (4.92 mmol) of 2-methyl-2-[(trimethylsilyl)-oxy]-3-pentanone was slowly dropped in. The solution was stirred at −70 °C for 20 min and then 453 μL (360 mg, 5 mmol) of isobutyraldehyde was added. After the solution was stirred at −70 °C for 1 min, saturated aqueous NH_4Cl was added and the mixture was allowed to warm to room temperature. After the

usual workup, 1.11 g (87%) of a pale yellow oil was isolated. This was dissolved in 100 mL of methanol and 37 mL of a 0.54 M solution of H_5IO_6 in water was added. This mixture was allowed to stand at room temperature for 16 h. The reaction mixture was evaporated to dryness and the residue was extracted with methylene chloride. The methylene chloride extracts were dried ($MgSO_4$) and evaporated to provide 369 mg (51% based on starting ketone) of a slightly yellow oil: ^1H NMR ($CDCl_3$) δ 3.71 (1 H, dd, J = 4, 7.5), 2.73 (1 H, dq, J = 4, 7), ~1.8 (1 H, m), 1.26 (3 H, d, J = 7), 1.08 (3 H, d, J = 5.5), 0.95 (3 H, d, J = 7.5).

Esterification of the hydroxy acid using excess diazomethane (prepared from *N*-methyl-*N*-nitrosourea and aqueous KOH) in ether afforded 473 mg (92%) of the hydroxy ester as an oil: ^1H NMR (CCl_4 + trace of HCO_2H) δ 3.73 (3 H, s), 3.58 (1 H, dd, J = 4.5, 7), ~2.6 (1 H, m), ~1.6 (1 H, m), 1.15 (3 H, d, J = 7), 0.98 (3 H, d, J = 6.5), 0.90 (3 H, d, J = 6.5).

***erythro*-3-Hydroxy-2-methyl-4-phenylbutanoic Acid (47).** A solution of lithium diisopropylamide (prepared from 1.41 mL (1.01 g, 10 mmol) of diisopropylamine and 7.14 mL of a 1.4 M solution of *n*-BuLi (10 mmol) in hexane) in 10 mL of THF was cooled to −70 °C and 1.76 g (9.34 mmol) of 2-[(trimethylsilyl)-oxy]-2-methyl-3-pentanone was slowly dropped in. After the solution was stirred at −70 °C for 20 min, 1.17 mL (1.20 g, 10 mmol) of phenylacetaldehyde was added. After 1 min, saturated aqueous NH_4Cl was added, and the mixture was allowed to warm to room temperature and then worked up in the usual manner. The crude product was taken up in 10 mL of 0.1 N methanolic HCl and stirred for 10 min, diluted with ether, washed with water and saturated NaCl, and dried ($MgSO_4$). Removal of solvent afforded 2.17 g of crude dihydroxy ketone. A portion of this material (1.88 g) was chromatographed on 200 g of silica gel, with 1:1 hexane/ether, to obtain 981 mg (51%) of pure adduct as a viscous oil: ^1H NMR ($CDCl_3$) δ 7.18 (5 H, s), 3.93 (1 H, ddd, J = 4, 6.5, 8), 3.2 (1 H, dq, J = 4, 7), 2.65 (2 H, m, AB portion of ABX), 1.35 (3 H, s), 1.25 (3 H, s), 1.18 (3 H, d, J = 7).

A solution of 456 mg (2 mmol) of H_5IO_6 in 4 mL of water was added to a solution of 118 mg (0.5 mmol) of this material in 10 mL of methanol. The mixture was allowed to stand at room temperature for 3 days. The solution was evaporated to dryness and the residue was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated to give 74 mg (76%) of a yellowish solid: ^1H NMR ($CDCl_3$) δ 7.27 (5 H, s), 6.2 (2 H, br s), 4.18 (1 H, m), 2.75 (2 H, m), 2.5 (1 H, m), 1.26 (3 H, d, J = 7). An analytical sample (mp 119–120 °C) was obtained by recrystallization from ethyl acetate. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.04; H, 7.24.

Methyl 3-Hydroxy-2-methyl-4-phenylpentanoate (48 and 49). A solution of lithium diisopropylamide (prepared from 2.82 mL (2.02 g, 20 mmol) of diisopropylamine and 13.3 mL of a 1.5 M solution of *n*-BuLi (20 mmol) in hexane) in 20 mL of THF was cooled to −70 °C and 3.76 g (20 mmol) of 2-methyl-2-[(trimethylsilyl)oxy]-3-pentanone was added over a period of ca. 15 min. The solution was stirred at −70 °C for an additional 20 min and then 2.66 mL (2.68 g, 20 mmol) of 2-phenylpropanal was added all at once. After 1 min, saturated aqueous NH_4Cl was added and the mixture was allowed to warm to room temperature. After the usual workup, the residue was treated with 40 mL of 0.1 N methanolic HCl for 15 min, 300 mL of ether was added, the layers were separated, and the ether layer was washed with water and saturated aqueous NaCl and evaporated. The residue was dissolved in 100 mL of methanol and a solution of 18.24 g (80 mmol) of H_5IO_6 in 160 mL of water was added. After the solution was stirred at room temperature for 13 h, an equal volume of water containing 3.7 mL of ethylene glycol was added, and this mixture was extracted exhaustively with ether. The ether extracts were extracted with dilute aqueous NaOH. The aqueous extract was acidified and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated to provide 2.71 g (65%) of a yellow oil which partially crystallized on standing. The crude hydroxy acid was taken up in 50 mL of ether and treated with an excess of an ethereal solution of diazomethane (prepared from *N*-methyl-*N*-nitrosourea and aqueous KOH). The unreacted diazomethane was quenched with acetic acid and the ether solution was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated. Distillation of the residue furnished 2.35 g (81%) of a colorless oil [bp 92 °C (bath temperature) (0.2 torr)]. Gas chromatographic analysis (8% Carbowax 20M) indicated an 81:19 mixture of esters **48** and **49**. The two hydroxy esters were separated by preparative gas chromatography with the same column. Each isomer was reduced to a diol with lithium aluminum hydride. The diol from the major isomer had mp 96.5–98 °C (lit.[41] mp 98–98.5 °C), and the diol from the minor isomer had mp 69–70.5 °C (lit.[41] mp 70.5–71 °C).

***cis*-4-Methyl-5-phenyloxazolidin-2-one (50).** To a solution of 733 mg (4.07 mmol) of hydroxy acid **45** in 25 mL of benzene was added 0.60 mL (4.31 mmol) of triethylamine and 0.87 mL (4.04 mmol) of diphenylphosphoryl azide. After the solution was refluxed under nitrogen for 30 h, the solution was cooled and washed with water, saturated $NaHCO_3$, 1% aqueous HCl, and brine. The solution was dried and concentrated in vacuo to obtain 721 mg (100%) of **50** (mp 142–144 °C) after recrystallization from benzene (lit.[53] mp 145–147 °C and 147–149 °C): ^1H NMR ($CDCl_3$) δ 7.33 (5 H, s), 5.67 (1 H, d, J = 8), 4.17 (1 H, m), 3.63 (1 H, d, J = 4), 0.77 (3 H, d, J = 7).

(±)-Ephedrine (51). A solution of 308 mg (1.74 mmol) of oxazolidone **50** in 6 mL of THF was slowly added to a solution of 126 mg (3.32 mmol) of $LiAlH_4$ in 10 mL of THF. The resulting mixture was refluxed overnight, cooled, and quenched by the cautious addition of 125 μL of water, 125 μL of 15% aqueous NaOH, and 380 μL of water. The mixture was filtered and the solvent removed in vacuo to obtain 270 mg (93%) of (±)-ephedrine, which was identical by ^1H NMR with an authentic sample of (−)-ephedrine. Recrystallization from hexane provided material melting at 77 °C (lit.[54] mp 79 °C).

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Registry No. 2a, 6531-45-9; **2b**, 554-12-1; **2c**, 70767-93-0; **2d**, 20487-40-5; **2e**, 1113-75-3; **2f**, 123-38-6; **2g**, 107-87-9; **2h**, 565-69-5; **2i**, 564-04-5; **2j**, 1660-05-5; **2k**, 30608-90-3; **2l**, 93-55-0; **2m**, 2040-15-5; **3b**, 72657-81-9; **3d**, 72657-82-0; **3e**, 72657-83-1; **3f**, 72657-84-2; **3g**, 72657-85-3; **3h**, 72657-86-4; **3i**, 72657-87-5; **3j**, 72657-88-6; **3k**, 72657-89-7; **3l**, 72657-90-0; **3m**, 72657-91-1; **4b**, 72657-92-2; **4d**, 72657-93-3; **4e**, 72657-94-4; **4f**, 72657-95-5; **4g**, 72657-96-6; **4h**, 72657-97-7; **4i**, 72657-98-8; **4j**, 72657-99-9; **4k**, 72658-00-5; **4l**, 72658-01-6; **4m**, 72658-02-7; **5b**, 72658-03-8; **5d**, 72658-04-9; **5e**, 72658-05-0; **5f**, 50300-18-0; **5g**, 51425-54-8; **5h**, 19980-41-7; **5i**, 61878-68-0; **5j**, 72658-06-1; **5k**, 72658-07-2; **5l**, 66323-99-7; **5m**, 72658-08-3; **6b**, 72658-09-4; **6d**, 72658-10-7; **6e**, 72658-11-8; **6f**, 39162-68-0; **6g**, 51425-53-7; **6h**, 19980-42-8; **6i**, 72658-12-9; **6j**, 72658-13-0; **6k**, 72658-14-1; **6l**, 71268-59-2; **6m**, 72658-15-2; **7a**, 66730-68-5; **7b**, 14366-89-3; **7c**, 70767-83-8; **7d**, 72658-16-3; **7e**, 72658-17-4; **7f**, 71699-31-5; **7g**, 71699-15-5; **7h**, 71699-19-9; **7i**, 36677-29-9; **7i** trichloroacetate, 72658-18-5; **7j**, 72658-19-6; **7k**, 72658-20-9; **7l**, 71908-03-7; **7m**, 61878-66-8; **8a**, 66730-67-4; **8b**, 17226-79-8; **8c**, 70767-88-3; **8d**, 72658-21-0; **8e**, 72658-22-1; **8f**, 71699-32-6; **8g**, 71699-16-6; **8h**, 71699-20-2; **8i**, 36677-30-2; **8i** trichloroacetate, 72658-23-2; **8j**, 61878-70-4; **8k**, 61878-71-5; **8l**, 71908-02-6; **8m**, 61878-67-9; **12**, 72658-24-3; **13**, 72658-25-4; **14**, 72658-26-5; **15**, 61878-68-0; **16**, 61878-69-1; **17**, 72658-27-6; **21** (M = Li), 72658-28-7; **21** (M = Zn), 72658-29-8; **22** (M = Li), 72658-30-1; **22** (M = Zn), 72658-31-2; **23** (M = Li), 72672-28-7; **23** (M = Zn), 72658-32-3; **24** (M = Li), 72658-33-4; **24** (M = Zn), 72658-34-5; **26**, 72658-35-6; **27**, 72658-36-7; **28**, 72658-37-8; **29**, 72658-38-9; **30**, 72658-39-0; **31**, 72691-73-7; **32**, 72748-19-7; **33**, 40630-06-6; **33** DNP, 54657-93-1; **35**, 72658-40-3; **36**, 72658-41-4; **38**, 2834-17-5; **40**, isomer 1, 72658-42-5; **40**, isomer 2, 72658-43-6; **41**, 72507-50-7; **42**, 72658-44-7; **43**, 72658-45-8; **44**, 71699-17-7; (±)-**15**, 64869-25-6; **46**, 72658-46-9; **47**, 72658-47-0; **48**, 72691-74-8; **49**,

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72691-75-9; (±)-50, 39663-75-7; (±)-51, 90-81-3; C_6H_5CHO, 100-52-7; p-$CH_3OC_6H_4CHO$, 123-11-5; $C_6H_5CH_2CHO$, 122-78-1; CCl_3CHO, 75-87-6; n-$C_5H_{11}CHO$, 66-25-1; propionic acid, 79-09-4; (β-methoxyethoxy)methyl chloride, 3970-21-6; 2,2-dimethyl-3-pentanol, 3970-62-5; 1-adamantanecarboxylic acid, 828-51-3; 2-ethyl-2-(trimethylsilyl)-1,3-dithiane, 72658-48-1; 2-ethyl-1,3-dithiane, 6007-23-4; mesitylene, 108-67-8; propionyl chloride, 79-03-8; diisopropylamine, 108-18-9; lithium diisopropylamide, 4111-54-0; tetra-n-butylammonium fluoride, 429-41-4; lithium hexamethyldisilylazide, 4039-32-1; 2-phenylpropanal, 93-53-8; methyl acrylate, 96-33-3; methyl 4-formylpentanoate, 40630-06-6; 2-hydroxybutyronitrile, 4476-02-2; ethylmagnesium bromide, 925-90-6; 2-methyl-2-[(trimethylsilyl)oxy]-3-pentanone, 72507-50-7; diazomethane, 334-88-3; 3-hydroxy-2,4-dimethylbenzenebutanoic acid, 72691-76-0.

A Formylation–Cyclization Method of Synthesis of Cycloalkenones from Unsaturated Ketones

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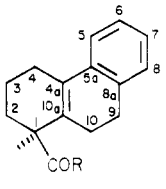
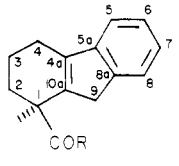
The acid-induced reaction of rigid β,γ- or γ-δ-unsaturated methyl ketones with methyl orthoformate is shown to yield alkenylcyclopentenones and -cyclohexenones, respectively. The use of ethyl orthoformate leads to more complex ring structures incorporating an ethoxy unit in both carbon–oxygen and carbon–carbon bonded form. The new structures are determined by ^{13}C NMR spectroscopy and their formation is justified on the basis of mechanistic arguments.

In continuation of studies of diterpene synthesis[1] it was important to obtain enol ethers of the methyl ketones **1b** and **2b**, which could be prepared from acids **1a**[2] and **2a**,[3]



1



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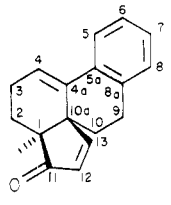
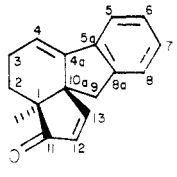


3

a, R = OH; b, R = Me



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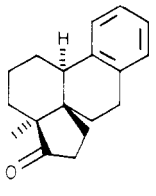

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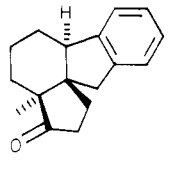
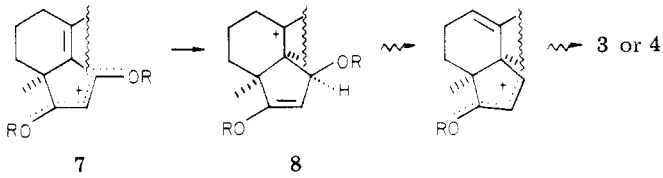


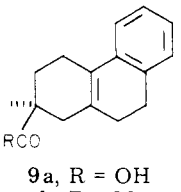
6

respectively, by consecutive treatments with oxalyl chloride, diethyl ethoxymagnesium malonate, and aqueous acid. Since the ketones were inert to orthoformic ester and acid catalysts under a variety of enol ether forming conditions,[4] they were exposed to an excess of trimethyl orthoformate in the presence of perchloric acid in the hope of forcing the desired reaction to occur, in spite of the possibility of α-formylation, a condensation known to take place under these reaction conditions.[5] The products were shown to be tetracyclic enones **3** and **4** by their spectral analyses and those of their tetrahydro products,[6] **5** and **6**, respectively. Whereas the forcing conditions had led to the enol ethers, these had interacted with dimethoxycarbonium perchlorate, the electrophilic product of the reaction of trimethyl orthoformate with perchloric acid, and subsequently lost methanol under acid catalysis. Even though the resultant 1,3-dialkoxyallyl cation should be stable until workup and then yield a β-alkoxyacrolein,[5] in **7** it faces a vicinal styrene double bond and thus reacts further, yielding styrene and cyclopentenone nuclei on workup.

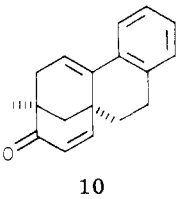


7 8 3 or 4

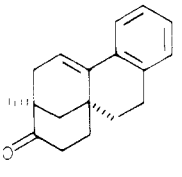
This simple formylation–cyclization procedure for cyclopentenone synthesis could be envisaged to be applicable to the construction of cyclohexenones by replacement of the starting β,γ-unsaturated ketone by a γ,δ-unsaturated one. As a consequence, the reaction was undertaken with methyl ketone **9b**, prepared from acid **9a** in the manner



9a, R = OH
b, R = Me



10



11

(1) U. R. Ghatak, S. K. Alam, and J. K. Ray, *J. Org. Chem.*, **43**, 4598 (1978).

(2) U. R. Ghatak, N. R. Chatterjee, A. K. Banerjee, J. Chakravarty, and R. E. Moore, *J. Org. Chem.*, **34**, 3739 (1969).

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(5) J. P. Dusza, J. P. Joseph, and S. Bernstein, *J. Am. Chem. Soc.*, **86**, 3908 (1964).

(6) The stereochemistry depicted in **5** and **6** is based on analogy with the steric course of hydrogenation of styrenes structurally related to **3** and **4**.[1]

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