Acyclic Stereoselection. 11. Double Stereodifferentiation as a Method for Achieving Superior Cram's Rule Selectivity in Aldol Condensations with Chiral Aldehydes[1]

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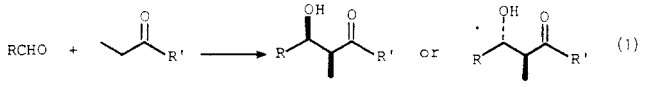
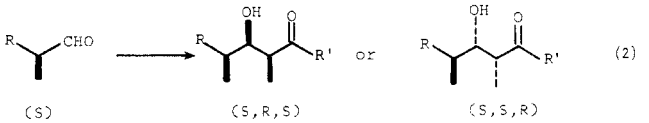
Double stereodifferentiation (double asymmetric induction) can be used to alter the effective diastereoface selectivity (Cram's rule selectivity) in additions to chiral aldehydes. The method has been demonstrated by the reactions of ketones **5** and **6** with the two enantiomers of glyceraldehyde acetonide (**46** and **47**) and also by the reaction of ketone **65** with aldehyde **46** with the two enantiomeric 1,2,3,4-tetramethoxybutanes **63** and **64** as solvents. In the former case, significant alteration of the Cram's rule selectivity is observed. With ketone **5**, the two erythro aldols are produced in a ratio of 1:1 with aldehyde **46** and 7:1 with aldehyde **47**. With ketone **6**, the double stereodifferentiation effect is greater; the two erythro aldols are formed in a ratio of 2:1 from aldehyde **46** and in a ratio of >30:1 from aldehyde **47**. Double stereodifferentiation with the chiral solvents **63** and **64** is more modest. However, the effect is still observed, and **65** and **46** react to give the two erythro aldols in ratios of 5.0:1 or 3.6:1 when **63** or **64** is employed as solvent.

The aldol condensation can show two distinct kinds of stereoselection. If two new asymmetric carbons are formed, as is often the case, they may have either the erythro or the threo relative configuration (eq 1).[2] We



(1)

refer to this kind of stereoselection as *simple diastereoselection*. A different kind of stereoselection is possible when either reactant is chiral. For example, addition of an enolate to a chiral aldehyde can give two erythro aldols, resulting from attack at either of the diastereotopic faces of the aldehyde (eq 2). Similarly, if the enolate is chiral

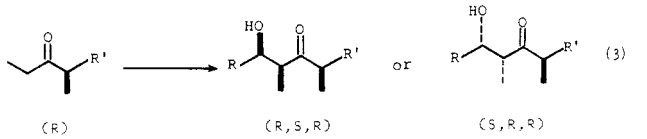


(2)

(S) (S,R,S) (S,S,R)

and the aldehyde achiral, there are also two erythro aldols resulting from attack at the diastereotopic faces of the enolate (eq 3). We term this kind of stereoselection *diastereoface selection*.

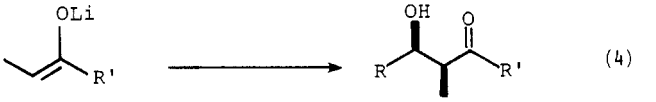
Several reagents are now available which give good simple diastereoselection in the aldol condensation.



(3)

(R) (R,S,R) (S,R,R)

Lithium enolates of ethyl carbonyl compounds having an additional bulky group attached to the carbonyl show good selectivity, with cis enolates giving erythro aldols (eq 4) and trans enolates giving threo aldols (eq 5).[4,5] Certain



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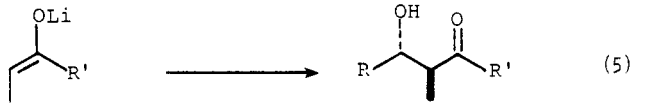
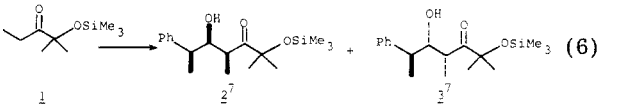


(5)

enol borinates show the same high selectivity even when a steric bias is not present.[6]

It is not so easy to achieve high diastereoface selection in additions to chiral aldehydes. For example, the enolate of ketone **1** reacts with α-phenylpropionaldehyde to give the two erythro aldols **2** and **3** in a ratio of 4:1[5] (eq 6).[5]



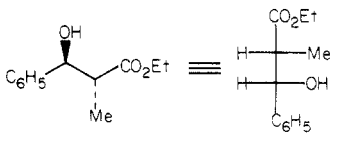
(6)

1 **2**[7] **3**[7]

Although this reaction does show some stereoselectivity, it is essential that stereoselectivity be improved if aldol technology is to be used in a consecutive manner for building up complex natural products like the macrolides

(1) (a) For paper 10 see C T. White and C. H. Heathcock, *J. Org. Chem.*, **46**, 191 (1981). (b) A part of this material has appeared in preliminary form: C. H. Heathcock and C. T. White, *J. Am. Chem. Soc.*, **101**, 7076 (1979).

(2) The convention employed for describing aldols is as follows: if the main chain is written in an extended (zig-zag) conformation, the diastereomer which has the C_α substituent and the C_β hydroxy both projecting either forward (bold bonds) or away from the viewer (dashed bonds) is called erythro. We realize that this is an arbitrary use of the erythro and threo descriptors. For example, the point has recently been made[3] that hydroxy ester i (threo in our usage) is in reality erythro, since the methyl and hydroxy groups both project to the right in a Fischer projection. However, it is our opinion that the latter definition of erythro and threo is just as arbitrary. To be perfectly accurate, it is only proper to employ these descriptors when referring to compounds having two asymmetric carbons which bear *two pairs* of identical substituents, as is the case with erythrose and threose themselves.



i

(3) S. Hanessian, 179th National Meeting of the American Chemical Society, Houston, TX, Mar 25, 1980.

(4) We prefer to use the stereochemical descriptors cis and trans, rather than *Z* and *E*, so that the same descriptor will always apply to an enolate of given geometry. In almost all cases, cis is equivalent to *Z*. The *E,Z* system, while unambiguous for indexing purposes, leads to confusion in discussions. For example, a given ester enolate is *Z* if $M^+ = Na^+$ but *E* if $M^+ = Li^+$ or if there is no counterion.

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

(6) (a) M. Hirama and S. Masamune, *Tetrahedron Lett.*, 2225 (1979); (b) M. Hirama, D. S. Garvey, L. D.-L. Lu, and S. Masamune, *ibid.*, 3937 (1979). (c) D. A. Evans, E. Vogel, and J. V. Nelson, *J. Am. Chem. Soc.*, **101**, 6120 (1979).

(7) Although this compound is racemic, only one enantiomer is depicted for convenience.

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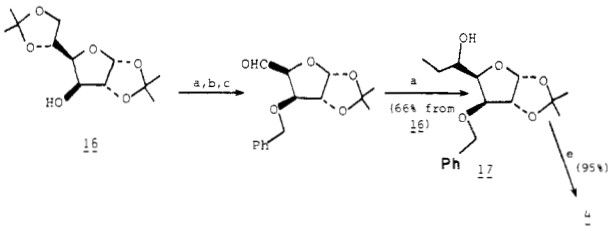
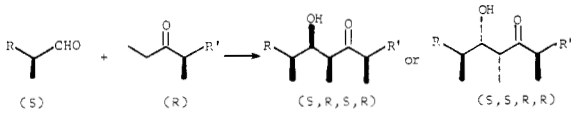
Scheme I[a]



[a] (a) NaH, THF, Me_2SO, $PhCH_2Cl$; (b) HOAc, H_2O; (c) $NaIO_4$; (d) C_2H_5MgBr; (e) PCC.

or the polyether ionophores. For example, a synthesis employing five aldol condensations, each proceeding with 80% stereoselectivity, can give an overall stereochemical yield of no more than 32%.

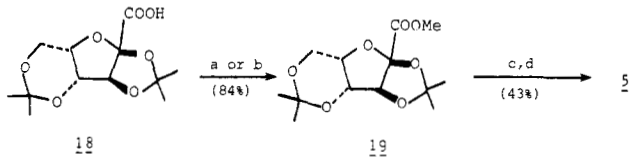
One way in which higher diastereoface selectivity might be realized is by use of double stereodifferentiation.[8,9] To illustrate how the technique would be applied in an aldol condensation, we return to the two kinds of diastereoface selection as illustrated in eq 2 and 3. Suppose that the *S* enantionmer of a given aldehyde gives mainly the (*S,R,S*)-aldol in its reactions with achiral enolates (eq 2). Suppose also that the *R* enantiomer of a given ketone gives mainly the (*R,S,R*)-aldol in its reactions with achiral aldehydes. If (*S*)-aldehyde is allowed to react with (*R*)-ketone, there are two erythro aldols which may be formed (*S,R,S,R* and *S,S,R,R*), as shown in eq 7. The former



(7)

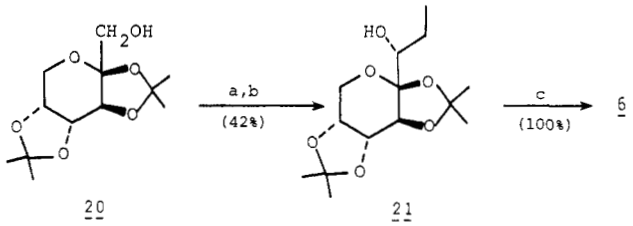
diastereomer should greatly predominate, since the *R,S* configuration at the two new centers is promoted by both aldehyde and enolate. To a first approximation, the (*S,R,S,R*):(*S,S,R,R*) ratio in eq 7 should be the product of the individual diastereoface selectivities of the aldehyde and the enolate in their reactions with comparable achiral reaction partners. Thus if (*S*)-aldehyde shows diastereoface selectivity of 5:1 favoring the (*S,R,S*)-aldol in reactions with achiral enolates and if (*R*)-ketone shows diastereoface selectivity of 5:1 favoring the (*R,S,R*)-aldol in its reactions with achiral aldehydes, then the (*S,R,S,R*):(*S,S,R,R*) ratio should be on the order of 25:1. Of course, reaction of (*S*)-aldehyde with (*S*)-ketone would be expected to lead to poorer diastereoface selectivity, from the standpoint of either reactant. For example, in the hypothetical case being discussed, the (*S,R,S,S*):(*S,S,R,S*) ratio would be about 1:1. We term this form of aldol stereoselection *double stereodifferentiation*, since the new chiral centers are introduced under the influence of two different chiral elements (in this example, the two reaction partners). Of course, double stereodifferentiation may also be achieved by the use of a chiral auxillary, such as the solvent. In this paper, we report the results of an investigation of the use of this strategy for enhancing diastereoface selection in the aldol condensation. Our method was to synthesize a series of optically active ethyl ketones and propionate esters derived from simple carbohydrates. We studied the aldol condensations of these compounds with benzaldehyde to determine if they show high simple diastereoselection (erythro, threo) and also to find if they show high inherent diastereoface selectivity. Three of the compounds have

Scheme II[a]



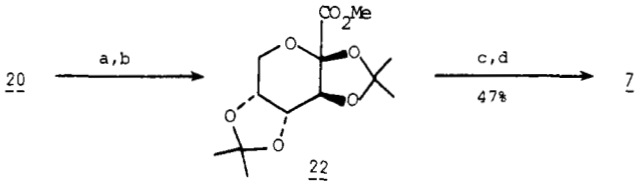
[a] (a) CH_2N_2, ether; (b) KH, MeI, DMF; (c) $CH_3CH(Li)SO_2Ph$, LDA, THF; (d) Al(Hg), H_2O, THF.

Scheme III[a]



[a] (a) $(CH_3)_2S$, NCS; (b) C_2H_5MgBr; (c) $(CH_3)_2S$, NCS.

Scheme IV[a]



[a] (a) $KMnO_4$, KOH; (b) MeI, DMF; (c) Me_3SiCH_2MgCl, ether; (d) NaOH, MeOH.

also been studied with the enantiomeric glyceraldehyde acetonides in double stereodifferentiation experiments.

Synthesis of Ketones and Esters

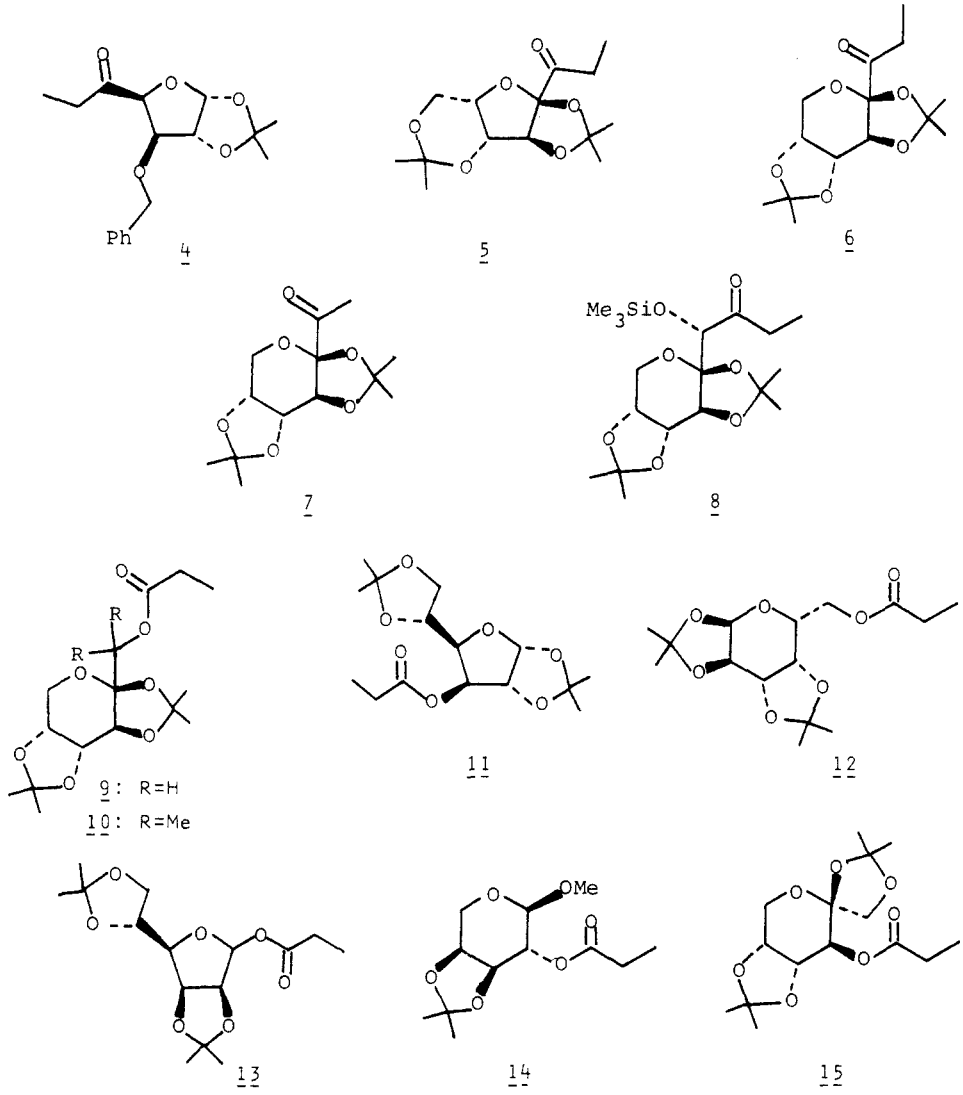
The compounds studied were ketones **4**–**8** and esters **9**–**15** (see Chart I). Ketone **4** was prepared from the bis(acetonide) of D-glucose (**16**)[10] as shown in Scheme I. After benzylation of the free hydroxyl, the 5,6-acetonide is hydrolyzed and the resulting diol cleaved with periodate. The resulting aldehyde reacts with ethylmagnesium bromide stereospecifically to give alcohol **17**, which is oxidized[11] to ketone **4**. The overall yield of **4** is 60% from **16**.

The preparation of **5** begins with diisopropylidenegulosonic acid (**18**, Scheme II), an intermediate in the industrial synthesis of vitamin C. Esterification is accomplished on a small scale by using diazomethane or on a larger scale by treating the potassium salt with methyl iodide. Ester **19** is converted into ethyl ketone **5** by reaction with the anion of ethyl phenyl sulfone, followed by reduction with aluminum amalgam. Ketone **5** is obtained in 36% overall yield from acid **18**.

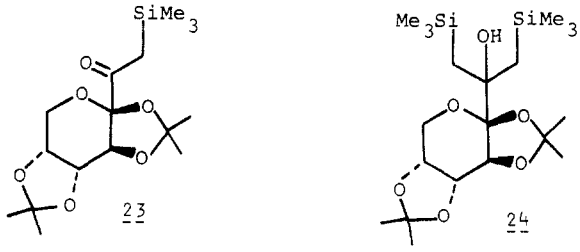
Diisopropylidenefructose (**20**)[12] is the starting material for the preparation of ketone **6** (Scheme III). The synthesis is straightforward and provides **6** in 42% overall yield. The methyl analogue of **6**, ketone **7**, was prepared from **20** as shown in Scheme IV. Oxidation of **20** with potassium permanganate affords the potassium salt of an acid which is directly treated with methyl iodide in DMF to obtain ester **22**. This ester reacts with 1.2 equiv of Grignard reagent derived from the commercially available (chloromethyl)trimethylsilane to provide a 4:1 mixture of

(8) A. Horeau, H.-B. Kagan, and J.-P. Vigneron, *Bull. Soc. Chim. Fr.*, 3795 (1968).
(9) Y. Izumi and A. Tai, "Stereodifferentiating Reactions", Kodanshar Ltd., Tokyo, Academic Press, New York, 1977.
(10) W. Glen, G. Myers, and G. Grant, *J. Chem. Soc.*, 2568 (1951).
(11) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(12) R. F. Brady, Jr., *Carbohydr. Res.*, 15, 35 (1970).

Chart I



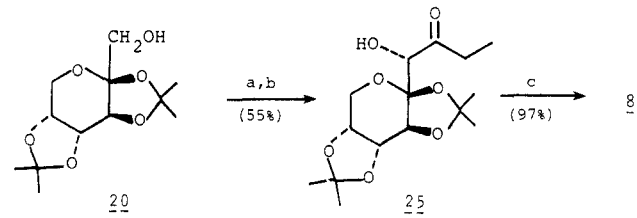
ketone **23** and tertiary alcohol **24**. Brief exposure of this mixture to methanolic NaOH affords ketone **7** after chromatographic purification.



The final ketone, compound **8**, was prepared from alcohol **20** (Scheme III) as outlined in Scheme V. Addition of 2-ethyl-1,3-dithiane[13] to the aldehyde obtained by oxidation of **20** occurs stereospecifically and in high yield to produce an adduct which is hydrolyzed and silylated to obtain **8**; the overall yield of **8** is 54% from **20**.

Propionate esters **9–15** were prepared by acylation of the corresponding alcohol in each case. For **9** and **11–15**, acylation was done by using propionyl chloride and triethylamine. For tertiary alkyl ester **10** this process is unsuccessful, and the ester must be made by formation of the lithium alkoxide (*n*-BuLi, THF, −78 °C) and reaction with propionyl chloride. Esters **9** and **11** were prepared from alcohols **16** and **20**. Alcohol **26**, the precursor to ester **10**, is conveniently prepared by reaction of ester **22** with 2 equiv of methyllithium in ether. Alcohols **27–30** are simple derivatives of galactose,[14] mannose,[15] arabinose,[16] and fructose,[12] respectively.

Scheme V[a]



[a] (a) $(CH_3)_2S$, NCS; (b) *i*, 2-lithio-2-ethyl-1,3-dithiane; *ii*, $HgCl_2$, H_2O, MeCN; (c) *N,O*-bis(trimethylsilyl)acetamide.

Simple Diastereoface Selection Experiments

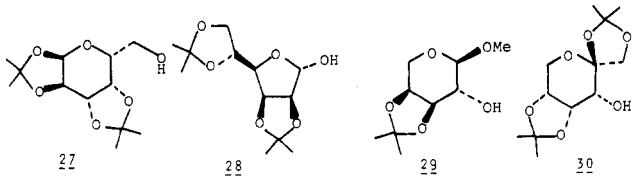
In order for the double-stereodifferentiation experiments to be significant, it is necessary that the two reaction

(13) D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975); E. J. Corey and B. W. Erickson, *ibid.*, **36**, 3553 (1971).

(14) A. L. Raymond and E. F. Schroeder, *J. Am. Chem. Soc.*, **70**, 2785 (1948).

(15) K. Freudenberg and R. M. Hixon, *Ber. Dtsch. Chem. Ges.*, 2119 (1923).

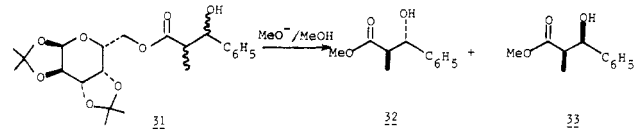
(16) M. A. Oldham and J. Honeyman, *J. Chem. Soc.*, 987 (1946).



27 28 29 30

partners each show some diastereoface selectivity in their reactions with achiral partners. As a measure of inherent diastereoface selectivity, we examined the condensation of compounds **4–15** with benzaldehyde. Diastereomer ratios were determined by ^{13}C NMR spectroscopy and in some cases were confirmed by analytical high-pressure LC. The relative stereochemistry at the two new centers (erythro, threo) was assigned on the basis of the ^{13}C NMR spectra of the mixtures, with the generalization that the α-methyl signals of erythro and threo aldols are in the ranges 8–12 and 11–14 ppm, respectively.[17] Data are shown in Table I. As expected,[5] the ketones give predominantly erythro aldols, while the esters give mainly threo isomers. Most of the compounds do not show high diastereoface selectivity, ratios in the range 1:1 to 2:1 being the rule. The most selective in this regard are ketone **6** and ester **9**, both of which show diastereoface selectivity of about 4:1. The single methyl ketone **7** shows no diastereoface selectivity.

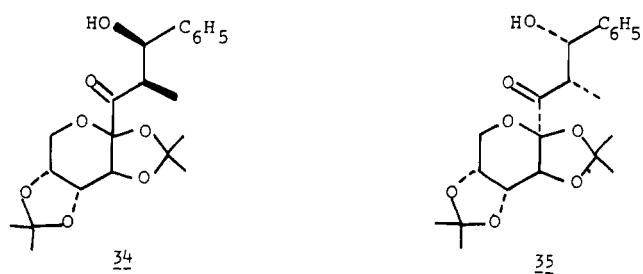
As shown in Table I, the esters studied all give complex mixtures. Although the components of some of these product mixtures can be resolved by using analytical high-pressure LC, we were unable to effect clean isomer separation using either preparative high-pressure LC or conventional column chromatography. In order to provide some additional evidence in favor of the validity of the ^{13}C NMR method[17] employed to assign erythro and threo stereostructures, we transesterified the product mixture (**31**) obtained from ester **12**. The *threo*- and *erythro*-β-



31 32 33

hydroxy esters **32** and **33**[5] were obtained in a ratio of 2:1, thus confirming the assignment made on the basis of ^{13}C NMR.

In contrast, the diastereomeric aldol products from ketones **4–8** are more easily separated. In most cases, the pure isomers can be obtained by simple chromatography. Because it gives only erythro products and shows moderate diastereoface selectivity, ketone **6** was selected for double-stereodifferentiation experiments (vida infra). For best interpretation of the results, it is required to know not only the inherent diastereoface selectivity toward an achiral aldehyde but also its sense. The structure of the major adduct (mp 82–84 °C) from **6** and benzaldehyde was shown to have structure **34** by single-crystal X-ray analysis



34 35

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

Table I. Condensation of Preformed Lithium Enolates of Compounds 4–15 with Benzaldehyde

compd	% erythro isomers	% threo isomers	simple diastereoselection[a]	diastereoface selection[b]
4	38, 36	26, 0	2.8	1.6–1.8
5	63, 37	0, 0	>20	1.7
6	79, 21	0, 0	>20	3.8
7	50, 50		na	1.0
8	60, 35	3, 2	19	1.6–1.7
9	20, 20	60, 0	0.67	4.0
10	19, 12	44, 25	0.45	1.3–1.7
11	33, 10	33, 24	0.75	1.3–1.9
12	16, 10	37, 36	0.35	1.1–1.2
13	22, 13	35, 30	0.54	1.1–1.2
14	9, 4	47, 39	0.15	1.0–1.3
15	10, 10	60, 20	0.20	2.4

[a] Expressed as the ratio erythro/threo. [b] Expressed as the ratio of total reaction at the two diastereotopic faces of the enolate. Uncertainty arises from the fact that full stereostructures are not known (see text).

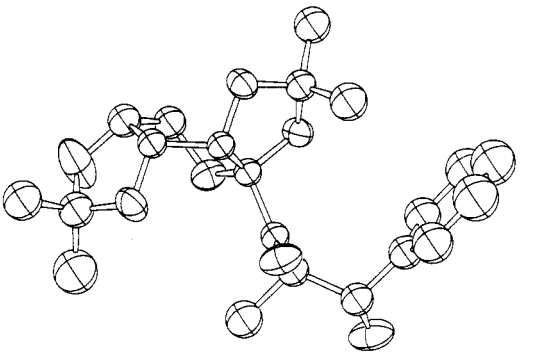


Figure 1. ORTEP representation of aldol **34**.

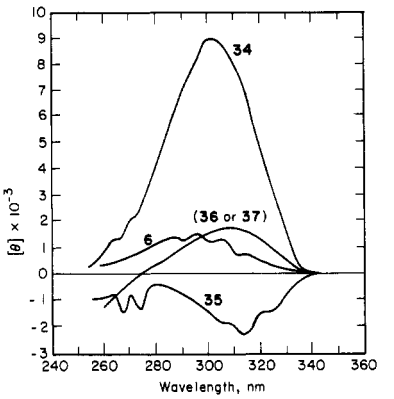
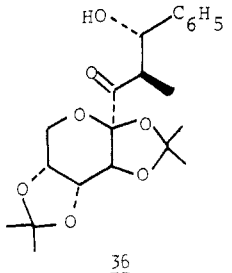


Figure 2. Circular dichroism curves of ketone **6** and aldols **34**, **35**, and **36** or **37**.

(Figure 1). Therefore, the minor isomer in this reaction (mp 105–107 °C) which is also an erythro isomer, must have structure **35**. Ketone **6** was also condensed with benzaldehyde via the zinc enolate.[18] After a reaction time of 1 h at 0 °C, the product was found to consist of three aldols in a ratio of 5:5:1. The two major products under these conditions are **34** and a threo diastereomer (mp 122–123.5 °C), which must be either **36** or **37**. The minor product is **35**.

The circular dichroism (CD) spectra of ketone **6**, aldols **34** and **35**, and the threo diastereomer (**36** or **37**) were also measured. Results are plotted in Figure 2. Note that aldol

(18) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).
(19) See C. Djerassi, "Optical Rotatory Dispersion; Applications to Organic Chemistry", McGraw-Hill, New York, 1960.



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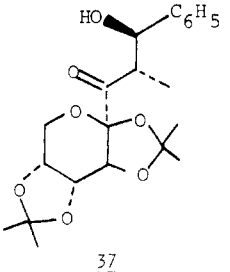
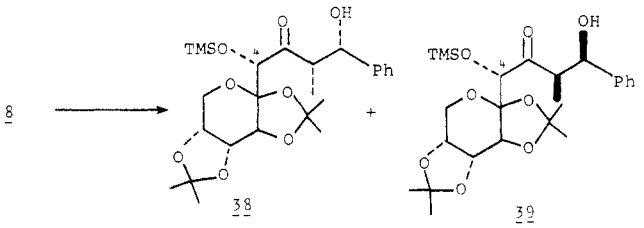


37

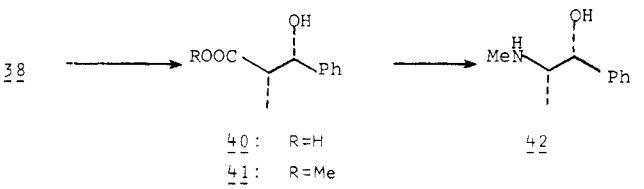
34 shows a maximum ($[\Theta]_{300}$ +8900) which is more positive than that of ketone 6 while aldol 35 shows a maximum ($[\Theta]_{300}$ −2500) which is more negative than that of 6. Figure 3 shows octant projections[19] of two fully staggered conformations of the major erythro aldol 34, assuming an intramolecular hydrogen bond within the aldol array. It would appear that either conformation of 34 would result in a more positive Cotton effect than is observed for the parent ketone 6. For example, in conformation a the α-methyl group is thrust strongly into the positive octant, while in conformation b it is the phenyl group which is tipped into the (+) octant. On the other hand, examination of Figure 4, which shows the two corresponding octant projections for the minor erythro aldol 35, shows that exactly the opposite effect is expected. In this case the methyl or phenyl is projected strongly into the negative octant. Thus, Figures 3 and 4 rationalize the observed Cotton effects of the two diastereomeric erythro aldols. More importantly, the agreement with experiment which is observed with 34 and 35 suggests that we can use the circular dichroism spectra as a criterion for stereostructure in other aldols derived from ketone 6. The threo aldols 36 and 37 are easier to analyze, since there should be only one stable hydrogen-bonded conformation of each. Figure 5 depicts octant projections of these two conformations. In neither case is either the methyl or phenyl group projected strongly into an octant. This analysis is consistent with the observation that [Θ] for the threo diastereomer is of about the same magnitude as is [Θ] for ketone 6 itself.

Stereostructures for the erythro aldol products 38 and 39, derived from the reaction of ketone 8 with benz-



8 → 38 + 39

aldehyde, were also determined. The major product of this reaction is readily obtained in pure form by preparative high-pressure LC. This material is cleaved by periodic acid to give optically active β-hydroxy acid 40 (mp 85–87 °C,



38 → 40: R=H; 41: R=Me → 42

$[\alpha]^{20}_D$ −29.5°). The configuration of 40 was established by converting it into (−)-ephedrine (42)[20] by the published procedure.[5] The minor erythro aldol 39 is obtained by

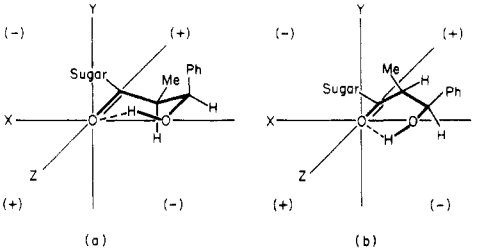


Figure 3. Octant projections for two conformations of aldol 34.

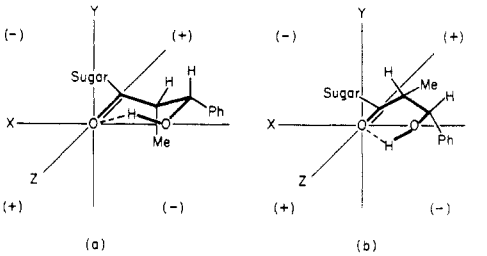


Figure 4. Octant projections for two conformations of aldol 35.

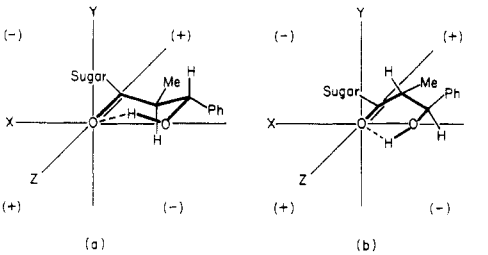
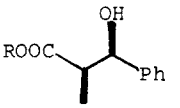


Figure 5. Octant projections for the threo aldols 36 and 37.

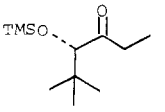
preparative high-pressure LC as a mixture with the two threo products. This mixture was cleaved to a mixture of β-hydroxy acids, which was esterified by treatment with diazomethane. The methyl esters were separated by chromatography to obtain methyl ester 44 which saponified



43: R=H

44: R=Me

to acid 43 (mp 87–88 °C, $[\alpha]^{20}_D$ +29.5). Note that this correlation establishes the stereochemistry of the two new chiral centers that are formed in the aldol condensation but does not rigorously establish the configuration of C-4, which is not determined in the preparation of ketone 8. The indicated stereostructure is assigned on the basis of the known sense of diastereoface selectivity of the related ketone 45.[21]



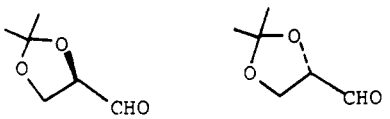
45

As a chiral aldehyde partner for our double stereodifferentiation experiment, we chose the acetonide of glyceraldehyde. The *R* enantiomer 46 was prepared by the method of Baer and Fischer.[22,23] The *S* enantiomer (47)

(20) M. Windholz, Ed., "The Merck Index", 9th ed., Merck and Co., Rathway, NJ, 1977.

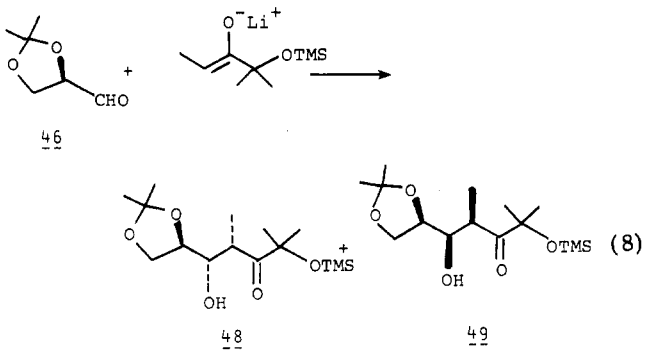
(21) C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, and D. VanDerveer, *J. Org. Chem.*, **45**, 3846 (1980).

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



46 47

was prepared from L-arabinose by the method of Baker.[23,24] We have recently shown that the inherent diastereoface selectivity of **46** and **47** is about 4.3:1 in the sense shown in eq 8.[21]

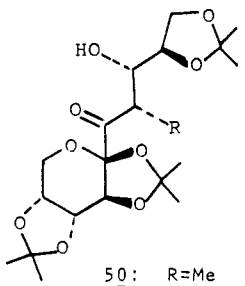


46 **48** **49** 4.3:1 (8)

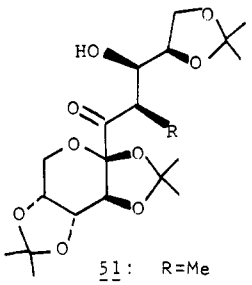
Stereodifferentiation with Two Chiral Reactants

Ketones **5–7** were selected for double-stereodifferentiation experiments. Compounds **5** and **6** were chosen because they both give only the two erythro adducts in their reactions with benzaldehyde and because they display a range of inherent diastereoface selectivities (1.7:1 to 3.8:1). Compound **7** was chosen to examine whether or not double stereodifferentiation can alter the net diastereoface selection in a methyl ketone. The data are presented in Table II.

Ketone **6**, which shows the highest diastereoface selectivity in its reaction with benzaldehyde (3.8:1), reacts with (*R*)-glyceraldehyde acetonide (**46**) to give three aldols in a ratio of 5.5:2.5:1. The two major products are easily obtained in a pure state by chromatography and were assigned structures **50** and **51**. Assignments were made



50: R=Me
58: R=H



51: R=Me
59: R=H

on the basis of the ^{13}C NMR spectra and circular dichroism curves of the two adducts. Both isomers were shown to have the erythro configuration by the ^{13}C NMR chemical shifts of the α-methyl resonances (12.6 and 10.7 ppm, respectively).[17] The CD curves of compounds **50** and **51** are shown in Figure 6. Since the minor erythro aldol has a Cotton effect which is more positive than that of ketone **6**, it is presumed to have the same chirality at the two new centers as aldol **34** and is accordingly assigned structure **51**. For the same reason, the major aldol, which shows a

(23) We thank Mr. Steven D. Young for preparing **46** and **47**.
(24) S. B. Baker, *J. Am. Chem. Soc.*, 74, 827 (1952).

Table II. Condensation of Preformed Lithium Enolates of Compounds 5–7 with Aldehydes 46 and 47

compd	diastereomeric aldol ratio: aldehyde **46**	aldehyde **47**
5	2.5:2.3:1	7:1:1
6	5.5:2.5:1	>30:1
7	1.8:1	1.6:1

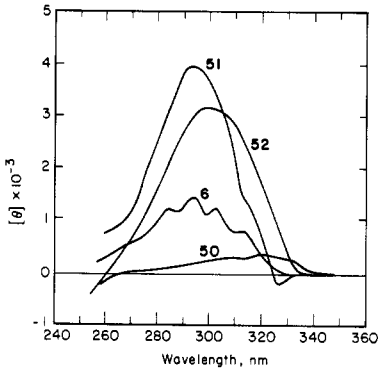
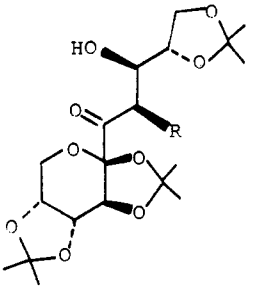


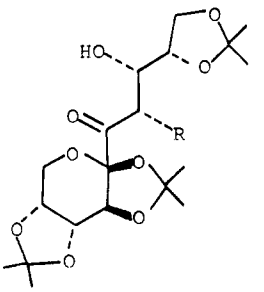
Figure 6. Circular dichroism curves for ketone **6** and aldols **50–52**.

Cotton effect more negative that that of ketone **6**, is assigned structure **50**.

On the other hand, ketone **6** reacts with (*S*)-glyceraldehyde acetonide (**47**) to give only a single aldol, within our limits of analysis. This adduct is erythro (^{13}C NMR α-methyl resonance of 10.5 ppm) and shows a distinct positive Cotton effect (Figure 6). Accordingly, this aldol is presumed to have structure **52**. The other erythro



52: R = Me
60: R=H

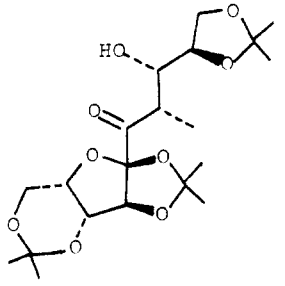


53: R=Me
61: R=H

adduct possible from the combination of ketone **6** with aldehyde **47**, aldol **53**, is formed to the extent of less than 3%. Thus, in the reaction of ketone **6** with the glyceraldehyde acetonides, the effective diastereoface selection changes from about 2:1 to greater than 30:1, depending upon which enantiomer of the aldehyde is employed.

Ketone **5**, which shows less inherent diastereoface selectivity than does ketone **6**, was also examined. With the (*R*)-aldehyde **46**, two erythro adducts (^{13}C NMR α-methyl resonances both at 11.5 ppm) are formed in a ratio of about 1:1. However, with the (*S*)-aldehyde **47**, the two erythro aldols (^{13}C NMR α-methyl resonances at 10.7 and 12.4 ppm) are produced in a ratio of 7:1. Thus, the principle of double stereodifferentiation is also demonstrated in this case, although the magnitude of the enhancement is less than in the first case discussed, since the ketone used shows lower inherent diastereoface selectivity than does ketone **6**. Although the diastereomeric aldols were not isolated in a pure state in this experiment and the stereostructures were not rigorously established, structures may be assigned by analogy to the results obtained in the condensations of ketone **6**. Thus, the two erythro aldols obtained from **5** and **46** must be **54** and **55** and those

obtained from 5 and 47 must be 56 and 57.



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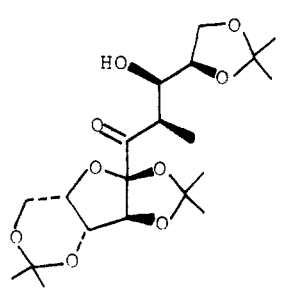

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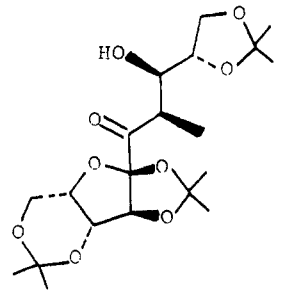

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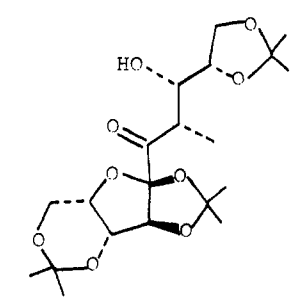
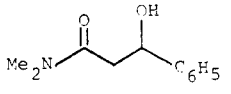


57

Methyl ketone 7 shows no inherent diastereoface selectivity with benzaldehyde. Thus, it was of interest to examine its reaction with the enantiomeric aldehydes 46 and 47. As shown by Table II, this ketone reacts with both aldehydes to give two aldols in a ratio range of 1.8:1 to 1.6:1. Thus, there is no double stereodifferentiation. The major aldol in each case is presumed to be that resulting from the preferred diastereoface attack on the aldehyde employed. Thus, we assume that the products from condensation of 7 with 46 are a 1.8:1 mixture of 58 and 59, while reaction of 7 with 47 gives a 1.6:1 mixture of 60 and 61.

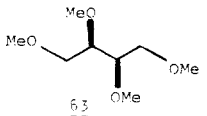
Double Stereodifferentiation with Chiral Solvents

Another way in which medicore diastereoface selection might be enhanced is by using a chiral solvent. For example, Seebach has shown that the lithium enolate of dimethylacetamide reacts with benzaldehyde in the presence of (+)-2,3-dimethoxy-1,4-bis(dimethylamino)butane to give β-hydroxy amide 62 with 14% enantiomeric excess (ee).[25]

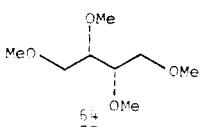


62

To explore the possibility of altering diastereoface selectivity by the use of chiral solvents, we employed the enantiomeric 1,2,3,4-tetramethoxybutanes 63 [(+)-TMB] and 64 [(−)-TMB].[26] To provide a calibration point, we



63



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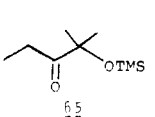

65

(25) D. Seebach, S. B. Schriftenreike des Fonds der Chemische Industrie, 1975.

Table III. Reaction of Ketone 65 with Aldehyde 46 in Various Solvents

solvent	erythro ratio (48:49)	% threo aldol
THF	4.3:1	4
(−)-TMB	5.0:1	14
(+)-TMB	3.6:1	17

first examined the reaction of ketone 65[5] with benzaldehyde using (−)-TMB as solvent. After periodic acid cleavage of the crude aldol product, a mixture of β-hydroxy acids 40 and 43 is obtained. The observed rotation shows 7% enantiomeric excess, favoring enantiomer 40.

The reaction of ketone 65 with (*R*)-glyceraldehyde acetonide (46) was carried out in (−)-TMB and (+)-TMB to determine the magnitude of double stereodifferentiation which is observed with such a combination. Results are shown in Table III. A small but distinct double stereodifferentiation is seen. The effect is small because the intrinsic stereodifferentiating ability of the tetramethoxybutanes is small, at least in reactions of α-alkoxy enolates. In both (−)-TMB and (+)-TMB the reaction of 65 with benzaldehyde gives a significant amount of a threo diastereomer (14–17%) in addition to the two erythro aldols 48 and 49. Although this threo isomer is also produced with THF as solvent, it amounts to only 4% of the total product in that case. The production of larger amounts of threo aldols, compared to THF, turns out to be a characteristic of solvents 63 and 64. This may be due to the fact that these polyoxygenated solvents effectively solvate this lithium ion, thus disturbing the six-center transition state which is assumed to account for the erythro–threo selectivity seen in this aldol condensation.[5]

The reaction of ketone 6 with benzaldehyde was also carried out in the enantiomeric tetramethoxybutanes. However, in both solvents the ratio of erythro aldols 34 and 35 (3.2:1) is virtually the same as when the condensation is carried out in THF (34/35 ratio of 3.8:1). The failure of ketone 6 to display enhanced diastereoface selectivity in one of the enantiomeric tetramethoxybutanes may be due to the fact there are many internal oxygens in 6 which can act as ligands for the lithium cation. Thus, the effect of the chiral auxillary is muted.

Finally, we studied the effect of the chiral auxillaries (+)-TMB and (−)-TMB on the reactions of ketone 6 with both 46 and 47. Results are shown in Table IV. Enhanced stereodifferentiation is not obtained. Instead, both condensations show reduced stereoselectivity in both solvents compared to that in THF. As in the reaction of ketone 65 with benzaldehyde (Table III), enhanced amounts of threo diastereomers are observed when tetramethoxybutane is used as solvent. Furthermore, the 2:1 ratio of 50 to 51 which is observed when 6 reacts with 46 in THF changes to 1:1.3 in (+)-TMB and 1:1.1 in (−)-TMB. Moreover, the reaction of 6 with 47, which affords a single aldol in THF, gives all four possible products in both tetramethoxybutanes, with the 52/53 ratio being about 4:1.

Conclusions

In this study we have demonstrated the utility of double stereodifferentiation as a logical method for enhancing the Cram's rule selectivity of a chiral aldehyde. The concept may be employed by using the correct (reinforcing) enantiomer of a chiral reagent (as in the reaction of 6 and

(26) D. Seebach, H.-O. Kalinowsky, B. Bastani, G. Cross, H. Daum, N. DuPreez, V. Ehrig, W. Langer, C. Nüssler, H.-A. Oei, and M. Schmidt, *Helv. Chim. Acta*, 60, 301 (1977).

Table IV. Reaction of Ketone 6 with Aldehydes 46 and 47 in Various Solvents

		aldol products, %						
aldehyde	solvent	50	51	threo[a] isomer	52	53	threo[a] isomer	threo[a] isomer
46	THF	61	28	11				
46	(+)-TMB	31	40	29				
46	(−)-TMB	34	37	29				
47	THF				>97			
47	(+)-TMB				61	15	15	8
47	(−)-TMB				57	16	15	12

[a] Structure unassigned.

47 or 5 and 47) or by using the correct enantiomer of a chiral auxillary (as in the reaction of 65 and 46 in (−)-TMB). In retrospect, the systems chosen for study in this work are probably not optimum for observing the maximum effect of double stereodifferentiation, since the ethyl ketones, the aldehyde, and the chiral solvents are all capable of chelating a lithium cation. More enhanced effects will probably be observed with other combinations of reaction partners.

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 sodium/benzophenone immediately prior to use. Triethylamine, tetramethylethylenediamine (TMEDA), tetramethylpiperidine, and diisopropylamine were distilled from calcium hydride and stored over 4-Å molecular sieves. Methylene chloride was distilled from P_2O_5 and stored over 4-Å molecular sieves. Pyridine was distilled from BaO and stored over 4-Å molecular sieves. Chlorotrimethylsilane was distilled from calcium hydride immediately prior to use. All reactions involving organometallic reagents or strong bases were conducted under a nitrogen atmosphere. Boiling points and melting points (Pyrex capillary) are uncorrected. Infrared (IR) spectra were determined with a Perkin-Elmer Model 297 infrared recording spectrophotometer. Ultraviolet (UV) spectra were determined with a Cary Model 118 ultraviolet spectrophotometer; results are expressed as λ_{max} in nanometers (log ϵ). ^{1}H NMR spectra were determined on the following spectrometers: Varian T-60, Varian EM-390, UCB 180 (a superconducting, 180-MHz, FT instrument), or UCB 250 (a superconducting 250-MHz, FT instrument). Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Significant ^{1}H NMR data are tabulated in the following order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) (in hertz). ^{13}C NMR spectra were measured at 25.14 MHz with a Nicolet TT-23 spectrometer or at 45.28 MHz on the UCB 180. Mass spectra were obtained with Atlas MS-12 and Consolidated 12-110B mass spectrometers. Mass spectral data are tabulated as m/e (intensity expressed as percent of total ion current). Gas–liquid partition chromatography (GLC) was done with Varian Aerograph A-90P, 920, and 940 gas chromatographs. High-pressure liquid chromatography (LC) was done with a Water Model ALC/GPC-244 liquid chromatograph (analytical) or a Waters PrepLC/System 500 (preparative). μ-Porasil columns were used unless otherwise indicated. Column chromatography was performed with Merck silica gel 60 (70–230-mesh ASTM). Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkely, CA.

3-*O*-Benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-α-L-*ido*-heptofuranose (17). To a stirred suspension of sodium hydride (920 mg, 38.5 mmol) in 40 mL of THF was added alcohol 16 (10.0 g, 38.5 mmol) in 20 mL of THF. Dimethyl sulfoxide (5 mL) was added, and the mixture was heated to reflux. Benzyl chloride (4.4 mL, 38.5 mmol) was added, and the mixture was allowed to reflux. The reaction may be followed by TLC (1:1 Et_2O–hexane): R_f 0.15 (alcohol 16), 0.48 (benzyl ether). After 3 h the reaction mixture was poured into 500 mL of water, and the water layer was saturated with sodium chloride and extracted three times with 50 mL of ether. The combined ether layers were washed four times with 50 mL of water, dried ($MgSO_4$) and evaporated to yield 13 g (95%) of 3-*O*-benzylidiisopropylidineglucose of sufficient purity for further transformations: ^{1}H NMR ($CDCl_3$) δ 1.30 (3 H, s), 1.40 (3 H, s), 1.45 (3 H, s), 1.52 (3 H, s), 5.88 (1 H, d, J = 4), 7.38 (5 H, br s). 3-*O*-Benzyldiisopropylidineglucose (12.8 g, 36.6 mol) was stirred with 60% aqueous acetic acid for 18 h at room temperature. The solvents were evaporated, and the residue was twice dissolved in toluene and evaporated to remove the acetic acid. The crude diol was dissolved in 150 mL of ethanol and treated with 16 mL of saturated sodium bicarbonate and 8.4 g of sodium periodate in 300 mL of water. After being stirred at room temperature for 2.5 h, the reaction mixture was diluted with ethanol, the salts were filtered, and the filtrate was concentrated in vacuo. The residue was again diluted with ethanol, filtered, and concentrated, and this procedure was repeated until no more salts precipitated after dilution with ethanol. The crude aldehyde was dissolved in 30 mL of THF and cooled to 5 °C. To this solution was added ethylmagnesium bromide (20 mL of a 2.95 M solution in ether, 59 mmol) dropwise over a 20-min period. After being stirred for 10 min, the reaction mixture was poured into 100 mL of saturated ammonium chloride, and the organics were separated. The aqueous layer was extracted one time with ether, and the combined organic layers (150 mL) were washed one time with 50 mL of 1 N HCl and one time with 50 mL of saturated sodium bicarbonate, dried ($MgSO_4$), and evaporated to yield 7.5 g (66%) of alcohol 17. This product may be chromatographed (2:1 hexane–ether on silica gel). Pure alcohol 17 slowly crystallizes: mp 65–70 °C; ^{1}H NMR ($CDCl_3$) δ 0.9 (3 H, m), 1.35 (3 H, br s), 1.50 (3 H, br s), 5.97 (1 H, d, J = 4), 7.37 (5 H, br s); IR (thin film) 3470, 1450, 1380, 1370, 1260, 1220, 1165, 1080, 1025 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.36; H, 7.94.

3-*O*-Benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-1,5-heptofuranodiulose (4). To a stirred suspension of pyridinium chlorochromate (2.94 g, 13.7 mmol) and sodium acetate (500 mg) in 20 mL of CH_2Cl_2 was added alcohol 17 (2.8 g, 9.1 mmol) in 10 mL of CH_2Cl_2. The reaction was monitored by TLC (1:1 ether–hexane): R_f 0.33 (alcohol 17), 0.62 (ketone 4). After 24 h another 1.0 g of pyridinium chlorochromate was added, and the solution was stirred for another 24 h. The reaction mixture was diluted with ether and decanted, and the black gummy residue was treated with several portions of ether. Filtration of the organics through a 3-in. pad of Florisil and evaporation of the solvents yielded 2.4 g of nearly pure ketone 4 as a colorless oil. The product was chromatographed (2:1 hexane–ether) on 120 g of Merck (70–230 mesh) silica gel. A yield of 1.8 g (65%) of pure ketone 4 was obtained: ^{1}H NMR ($CDCl_3$) δ 1.08 (3 H, t, J = 7.5), 1.39 (3 H, s), 1.54 (3 H, s), 2.65 (2 H, q, J = 7.5), 4.32 (1 H, d, J = 4), 6.10 (1 H, d, J = 4), 7.37 (5 H, br s); (IR film) 1720, 1455, 1385, 1375, 1220, 1165, 1080, 1025 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 208.4, 136.8, 128.1, 127.7, 127.3, 111.9, 105.7, 85.1, 83.6, 81.7, 72.2, 33.2, 26.6, 26.0, 6.3. Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.46; H, 7.21.

Methyl 2,3:4,6-Di-*O*-isopropylidene-α-L-*xylo*-2-hexulofuranosonate (19). Method A. In a 250-mL Erlenmeyer flask were placed 30 mL of 40% aqueous KOH and 100 mL of ether. The mixture was cooled in an ice bath, and 10.0 g of *N*-methyl-*N*-nitrosourea was added portionwise with swirling. After the mixture was swirled an additional 2 min in the ice bath, the ether layer was decanted. The aqueous layer was twice more treated with 25 mL of ether and then decanted. The cold yellow

ether solution was added to a solution of 5.0 g of acid **18** in 40 mL of methanol also cooled in an ice bath. The yellow solution was gently warmed on a hot plate while N_2 was bubbled through the solution until the volume had been reduced by half. The nearly colorless solution was evaporated in vacuo to give a quantitative yield of ester **19**. The ^1H NMR spectrum is identical with that reported in the literature.[27]

Method B. A 250-mL flask was charged with diisopropylidenegulosonic acid (**18**; 29.0 g, 0.100 mol), potassium fluoride dihydrate (28.2 g, 0.300 mol), methyl iodide (46.2 g, 18.7 mL, 0.300 mol), and 100 mL of DMF. The mixture was stirred for 18 h and poured into 700 mL of water. After the reaction mixture was extracted four times with 100 mL of ether, the organic layers were combined, washed two times with 100 mL of water, dried (Na_2SO_4), and evaporated to yield 24.3 (84%) of ester **19**.[27]

1,2-Dideoxy-2,3:4,6-di-*O*-isopropylidene-α-L-*xylo*-2,3-octofuranodiulose (5). To a solution of ethyl phenyl sulfone (14.2 g, 83.3 mmol) and diisopropylamine (11.7 mL, 83.3 mmol) in 200 mL of THF was added *n*-butyllithium (105 mL of a 1.58 M solution in hexane, 167 mmol). The addition of *n*-butyllithium was exothermic, and the temperature of the reaction reached −50 °C at one point during the addition. After the mixture was stirred at −70 to −75 °C for 1 h, the ester **19** (24.0 g, 83.3 mmol) in 100 mL of THF was added dropwise over 30 min. After an additional 15 min at −75 °C, the cold bath was removed (the reaction mixture was yellow) and the reaction stirred another 30 min, with the final temperature reaching −10 °C. At −40 °C the reaction began to darken, and by the time it reached −10 °C the reaction mixture was black. This was poured into 700 mL of saturated ammonium chloride. The organic layer was removed, and the aqueous layer was extracted two times with 250 mL of ether. The deep red organic layers were combined, dried ($MgSO_4$), and evaporated to give 36 g of crude sulfone as a dark, foamy, thick oil. The product is approximately a 1:1 mixture of diastereomers: TLC (2:1 ether–hexanes) R_f 0.32, 0.29; IR (3% solution in $CHCl_3$) 1740, 1445, 1380, 1375, 1310, 1300, 1140, 1100 cm^{-1}.

The crude sulfone (36 g) was dissolved in 2 L of 10% aqueous THF. To this solution was added Al(Hg) (made from 22 g of Al foil cut into 2 × 2 cm squares treated with 2% aqueous $HgCl_2$ for 30 s and washed with H_2O, EtOH, and ether), and the resulting heterogeneous mixture was heated under gentle reflux with vigorous mechanical stirring. After 1 h, the reaction mixture was filtered through Celite. The collected salts were washed with THF, and the filtrate was concentrated in vacuo. The residue was extracted two times with 250 mL of ether. The ether layers were combined, dried (Na_2SO_4), and evaporated to give 24 g of a pale yellow, thick oil. The crude product was chromatographed by high-pressure LC with elution with 35% ethyl acetate in hexane. A yield of 10.2 g (43% based on methyl ester **19**) of ketone **5** was obtained: IR (3% solution in $CHCl_3$) 1715, 1380, 1375, 1120, 1090, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (3 H, t, J = 6.5), 1.33 (3 H, s), 1.43 (3 H, s), 1.47 (3 H, s), 1.53 (3 H, s), 2.9 (2 H, m). Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.74. Found: C, 58.87; H, 7.75.

1,2-Dideoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*arabino*-*glycero*-4-octulopyranose (21). To a solution of *N*-chlorosuccinimide (2.0 g, 15 mmol) in 63 mL of dry CH_2Cl_2 at 0 °C was added 1.5 mL (30 mmol) of freshly distilled dimethyl sufide. A fine white precipitate resulted. After the mixture was cooled to −25 to −30°, diacetone fructose **20** (2.6 g, 10 mmol) in 7 mL of dry CH_2Cl_2 was added at a rate such that the temperature was maintained below −25 °C, and the mixture was stirred for 2 h at −20 to −30 °C. Triethylamine (1.6 mL) was added, and the reaction mixture was stirred for 5 min and poured into 200 mL of H_2O. The organic layer was separated, and the aqueous layer was extracted two times with 75 mL of CH_2Cl_2. The CH_2Cl_2 layers were combined, dried (Na_2SO_4), and evaporated to give the aldehyde as a colorless oil contaminated with a small amount of succinimide. The product was placed on a short (12 × 4 cm) silica gel column and eluted with 70% ether in hexanes. A yield of 1.85 g (72%) of the aldehyde was obtained. The aldehyde prepared by this method is contaminated with varying amounts of hydrate: IR (thin film) 3480, 1750, 1380, 1250, 1210, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (3 H, s), 1.39 (3 H, s), 1.41 (3 H, s), 1.57 (3 H, s), 9.40 (1 H, s).

To a solution of aldehyde (1.85 g, 7.2 mmol) in 20 mL of dry THF was added 6 mL (17 mmol) of a 2.9 M solution of ethylmagnesium bromide in ether with ice-bath cooling. After the addition, the bath was removed and the mixture stirred for 1 h. This was poured into 50 mL of saturated NH_4Cl, the organic layer was removed, and the aqueous layer was extracted two times with 40 mL of ether. The combined organic layers were washed one time with 50 mL of saturated $NaHCO_3$, dried (Na_2SO_4), and evaporated to yield 1.8 g of alcohol **21** as a colorless oil. After chromatography on silica gel, eluted with 1:1 ether–hexanes, a yield of 1.2 g of pure **21** (58%, 42% based on alcohol **20**) was obtained: IR (thin film) 3500, 1380, 1370, 1250, 1210, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (3 H, s), 1.43 (3 H, s), 1.47 (3 H, s), 1.55 (3 H, s). Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.67; H, 8.44.

1,2-Dideoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*arabino*-3,4-octopyranodiulose (6). To a solution of *N*-chlorosuccinimide (0.71 g, 5.3 mmol) in 22 mL of CH_2Cl_2 cooled to 0 °C was added dimethyl sulfide (0.52 mL, 7.0 mmol). The resultant fluffy white slurry was cooled to −25 °C, and alcohol **21** (1.0 g, 3.5 mmol) dissolved in 3 mL of CH_2Cl was added at a rate such that the temperature stayed below −25 °C. After the temperature had been maintained between −15 and −30 °C for 2.75 h, triethylamine (0.6 mL, 4 mmol) was added, and after 5 min the reaction was poured into 100 mL of water. The CH_2Cl_2 layer was removed, and the aqueous layer was extracted two times with 50 mL of CH_2Cl_2. The CH_2Cl_2 layers were combined, dried (Na_2SO_4), and evaporated to give 1.0 g (100%) of nearly pure ketone **6** as a colorless oil: $[\alpha]_D$ −61.9 (*c* 1.66, acetone); ^1H NMR δ 1.07 (3 H, t, J = 7), 1.35 (3 H, s), 1.42 (6 H, br s), 1.55 (3 H, s), 2.76 (2 H, q, J = 7), 3.8–4.8 (5 H, m); IR (thin film) 2995, 2945, 1730, 1380, 1370, 1255, 1215, 1180, 1170, 990, 980, 935, 920, 885, 875, 760, 740 cm^{-1}; ^{13}C NMR δ 205.2, 109.6, 108.9, 101.8, 70.7, 70.4, 70.2, 61.3, 30.2, 26.0, 25.9, 24.7, 24.1, 7.3. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.75; H, 7.74. Found: C, 59.02; H, 7.80.

Methyl 2,3:4,5-Di-*O*-isopropylidine-α-D-*arabino*-2-hexulopyranosonate (22). In a 6-L Erlenmeyer flask was dissolved alcohol **20** (97 g, 0.31 mol) in a mixture of 4.3 L of water and 100 mL of 8 N KOH. Potassium permanganate was added (290 g, 1.8 mol) portionwise (58 g each hour for 5 h). This mixture was stirred for 24 h at room temperature. The excess potassium permanganate was destroyed by the addition of a small amount of sodium thiosulfate. The reaction mixture was filtered through Celite, and the brown MnO_2 was washed with water. Carbon dioxide was bubbled through the filtrate until it became neutral to phenolphthalein, and the water was evaporated in vacuo (bath temperature <55 °C). The residue was extracted two times with 300 mL of boiling 95% ethanol. The ethanol was evaporated to yield 90 g of the potassium carboxylate as a gummy white solid. This material was dissolved in 500 mL of dimethylformamide and treated with methyl iodide (70 mL). After 30 h the reaction mixture was poured into 3.5 L of water and extracted four times with 500 mL of ether. The organics were dried (Na_2SO_4) and evaporated to give 61 g of crude ester **22**. The crude product was distilled to yield pure ester **22**: 46.6 g (43.4%); bp 103–105 °C (1.2×10^{-5} torr); IR (thin film) 1750, 1430, 1390, 1380, 1290, 1260, 1220, 1190, 1170, 1120, 1080, 1000, 900, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (3 H, s), 1.43 (3 H, s), 1.46 (3 H, s), 3.83 (3 H, s). These spectra are identical with those reported.[27]

1-Deoxy-3,4:5,6-di-*O*-isopropylidene-β-D-*arabino*-2,3-heptopyranodiulose (7). To a stirring suspension of 1.2 g (50 mmol) of magnesium turnings in 30 mL of ether at room temperature was added (chloromethyl)trimethylsilane (7.0 mL, 6.1 g, 50 mmol) in 15 mL ether over a 2-h period (syringe pump). Initial formation of the Grignard reagent may be slow. The addition of a small amount of ethylmagnesium bromide or ethyl bromide during the early stages of the addition is usually sufficient to initiate the reaction. After all the silane was added, the reaction mixture was stirred until all the magnesium had been consumed, usually 1 h. The solution of the Grignard reagent was added slowly, via syringe pump, to a solution of ester **22** (7.2 g, 25 mmol) in 30 mL of ether. The reaction may be followed by TLC (40% ether in hexanes): R_f 0.24 (ester **22**), 0.50 (β-oxosilane **23**), 0.61 (bisaddition product **24**). The addition was stopped when the starting ester was nearly

(27) J. Smejkal and L. Kaxoda, *Collect. Czech. Chem. Commun.*, **38**, 1981 (1973).

or completely consumed. The reaction mixture was poured into 300 mL of saturated ammonium chloride. The organic layer was removed, and the aqueous layer was extracted two times with ether. The organic layers were combined, dried ($CaCl_2$), and evaporated to give 8.1 g of a pale yellow oil which consists of a separable mixture of ketone **23** and alcohol **24**. A pure sample of the β-oxosilane **23** was obtained as a colorless oil by chromatography on silica gel, eluted with 40% ether in hexanes: IR (thin film) 1705, 1380, 1375, 1225, 1210, 1070, 1000, 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.12 (9 H, s), 1.34 (3 H, s), 1.38 (3 H, s), 1.40 (3 H, s), 1.50 (3 H, s), 2.18 (1 H, d, J = 11), 2.73 (1 H, d, J = 11). Anal. Calcd for $C_{16}H_{28}O_6Si$: C, 55.79; H, 8.19. Found: C, 56.02; H, 8.29.

Alcohol **24**: mp 46–50 °C; IR (thin film) 3600 (spike), 3550 (br), 1380, 1375, 1250, 1210, 1080, 1060, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.19 (9 H, s), 0.13 (9 H, s), 1.40 (3 H, s), 1.48 (3 H, s), 1.50 (3 H, s), 1.57 (3 H, s). Anal. Calcd for $C_{20}H_{40}O_6Si_2$: C, 55.52; H, 9.32. Found: C, 55.56; H, 9.16.

To a solution of the crude product from above (8.1 g) in 100 mL of methanol was added 1.2 g (30 mmol) of sodium hydroxide in 20 mL of methanol. After 5 min, the methanol was evaporated in vacuo. The residue was partitioned between ether and water. The ether layer was removed, and the aqueous layer was extracted one time with ether. The organics were combined, dried ($CaCl_2$), and evaporated to give 4.9 g of a nearly colorless oil which was chromatographed on 300 g of silica gel by elution with 25% ether in hexanes. A yield of 3.2 g (47% based on ester **22**) of pure ketone **7** was obtained as a colorless oil: IR (thin film) 1735, 1380, 1375, 1210, 1070, 990, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (3 H, s), 1.40 (3 H, s), 1.53 (3 H, s), 2.32 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 24.1, 24.6, 25.9, 61.4, 70.1, 70.3, 101.6, 109.0, 109.5, 202.2. Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.52; H, 7.27.

1,2-Dideoxy-5,6:7,8-di-*O*-isopropylidene-β-D-*arabino*-*glycero*-3,5-nonopyranodioulose (25). To a solution of 2-ethyl-1,3-dithiane[13] (1.72 g, 11.6 mmol) in 35 mL of dry THF at −40 °C was added 7.40 mL (11.6 mmol) of a 1.58 M solution of *n*-butyllithium in hexane. The reaction was allowed to warm to −20 °C and maintained at −20 °C for 105 min. The mixture was cooled to −70 °C and maintained at −20 °C for 105 min. The mixture was cooled to −70 °C, and a solution of the aldehyde (prepared as described above; 3.0 g, 11.6 mmol) in 2 mL of dry THF was added at a rate such that the temperature was maintained below −55 °C. The cooling bath was removed, and the reaction was stirred 1.5 h (final temperature was −10 °C). The reaction mixture was poured into 250 mL of H_2O and extracted three times with CH_2Cl_2. The CH_2Cl_2 layers were combined, washed one time with H_2O, one time with 4% NaOH, and one time with saturated NaCl, dried (K_2CO_3), and evaporated to give 4.55 g (95%) of the nearly pure adduct as a colorless oil. The product was sufficiently pure for the following transformation: IR (thin film) 3470, 1380, 1370, 1250, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (3 H, t, J = 7), 1.35 (3 H, s), 1.47 (3 H, s), 1.55 (3 H, s), 1.9 (2 H, m), 2.22 (2 H, q, J = 7), 2.8 (4 H, m), 3.2 (1 H, d, J = 6), 3.93 (1 H, d, J = 6).

To a solution of $HgCl_2$ (6.6 g, 24 mmol) in 165 mL of CH_3CN/H_2O (4/1) was added a solution of the dithiane (4.55 g, 11.2 mmol) in 110 mL of CH_3CN/H_2O (4/1). Red HgO (2.7 g, 12 mmol) was added, and the resulting mixture was heated at reflux for 4.5 h. After cooling, the mixture was filtered through Celite, and the collected solids were washed with 500 mL of CH_2Cl_2/hexane (1/1). The organic layer was separated and washed two times with 350 mL of 5 M NH_4OAc, one time with H_2O, and one time with saturated NaCl. After the solution was dried (Na_2SO_4) and evaporated, a yield of 2.7 g (76%) of ketone **25** was obtained. An analytical sample was prepared by chromatography on silica gel eluted with 35% ether in hexanes: IR (thin film) 3450, 1710, 1380, 1370, 1250, 1210, 1105, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (3 H, t, J = 7), 1.40 (6 H, s), 1.48 (3 H, s), 1.53 (3 H, s), 2.6 (2 H, m). Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 56.62; H, 7.64.

1,2-Dideoxy-5,6:7,9-di-*O*-isopropylidene-4-*O*-(trimethylsilyl)-β-D-*arabinoglycero*-3,5-nonapyranodiulose (8). The hydroxy ketone **25** (0.10 g, 0.32 mmol) was mixed with bis(trimethylsilyl)acetamide (0.05 mL, 0.2 mmol) and the mixture heated at 95 °C for 22 h. The reaction product was partitioned between hexanes and water. After removal of the organic layer, the aqueous layer was extracted one time with hexanes. The hexane layers were combined, dried (Na_2SO_4) and evaporated to give 0.12 g (97%) of **8** as a nearly colorless oil which slowly crystallizes just below room temperature: bp 122–123 °C (0.02 torr); IR (thin film) 1720, 1380, 1370, 1250, 1215, 1110, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.17 (9 H, s), 1.02 (3 H, t, J = 7), 1.33 (3 H, s), 1.43 (3 H, s), 1.52 (6 H, s), 2.67 (2 H, dq, J = 3, 7); ^{13}C NMR ($CDCl_3$) δ −0.3, 7.4, 24.3, 25.5, 25.9, 26.6, 32.3, 61.3, 70.1, 70.5, 71.0, 78.9, 103.4, 109.0, 109.2, 209.1. Anal. Calcd for $C_{18}H_{32}O_7Si$: C, 55.64; H, 8.34. Found: C, 55.73; H, 8.30.

Table V

compd	procedure	reaction time, h	purified yield, %	mp, °C
9	A	18	77	oil
10	B	4	62	oil
11	A	18	65	oil
12	A	1	76	oil
13	A	1	70	42–44
14	A	2	66	83–85
15	A	5 (at reflux)	70	oil

2,3:4,5-Di-*O*-isopropylidene-1,1-di-*C*-methyl-β-D-fructopyranose (26). To a solution of ester **22** (2.9 g, 10 mmol) in 25 mL of dry THF was added CH_3Li (15 mL of a 1.5 M solution in ether, 22.5 mmol) dropwise, with an ice bath being used to control the reaction temperature during the addition. After being stirred for 6 h at room temperature, the reaction mixture was poured into 100 mL of saturated NH_4Cl. The organic layer was removed, and the aqueous layer was extracted one time with ether. The organics were combined, washed one time with saturated $NaHCO_3$, dried (Na_2SO_4), and evaporated to yield 2.8 g of alcohol **26** (96%) as a colorless oil: IR (thin film) 3500, 1380, 1370, 1250, 1210, 1115, 1085, 900, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (3 H, s), 1.37 (6 H, s), 1.43 (3 H, s), 1.48 (3 H, s), 1.55 (3 H, s). Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.67; H, 8.30.

General Procedure for the Preparation of Esters 9–15. Procedure A. To a solution of the alcohol (10 mmol) in 30 mL of ether were added triethylamine (22 mmol) and propionyl chloride (15 mmol). Ice-bath cooling of the reaction was required during the addition of propionyl chloride. After being stirred for the desired length of time (Table V), the reaction mixture was poured into 50 mL of saturated $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), and evaporated to give the propionate ester.

Procedure B. To a solution of the alcohol (10 mmol) in 30 mL of THF cooled to 0 °C was added *n*-butyllithium (10 mmol, 1.5 M solution in hexane). After the mixture was stirred for 30 min at 0 °C, propionyl chloride (13 mmol) was added, and the reaction mixture was stirred at room temperature for the prescribed time (Table V). The mixture was then poured into 50 mL of saturated $NaHCO_3$ and diluted with 50 mL of ether. The organic layer was separated, dried (K_2CO_3) and evaporated to give the crude propionate ester.

2,3:4,5-Di-*O*-isopropylidene-1-*O*-propionyl-β-D-fructopyranose (9). Crude ester **9** was obtained in 100% yield on an 11-mmol scale. It was purified by high-pressure LC with elution with 15% ether in hexanes which gave 2.62 g (77%) of pure ester **9**: IR (film) 1745, 1380, 1375, 1250, 1210, 1180, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (3 H, t, J = 8), 1.37 (3 H, s), 1.43 (3 H, s), 1.50 (3 H, s), 1.57 (3 H, s), 2.38 (2 H, q, J = 8). Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 57.26; H, 7.69.

2,3:4,5-Di-*O*-isopropylidene-1,1-di-*C*-methyl-1-*O*-propionyl-β-D-fructopyranose (10). Crude ester **10** was obtained in 91% yield on an 8.5-mmol scale. The crude product was purified by chromatography on silica gel eluted with 30% ether in hexanes which gave 1.8 g (62%) of pure **10**: IR (thin film) 1740, 1380, 1370, 1250, 1220, 1210, 1200, 1180, 1160, 1155, 1150, 1120, 1080, 1070, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (3 H, t, J = 8), 1.35 (3 H, s), 1.48 (6 H, s), 1.55 (3 H, s), 1.65 (3 H, s), 1.68 (3 H, s), 2.28 (2 H, q, J = 8). Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.29; H, 8.17. Found: C, 59.47; H, 8.21.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-propionyl-α-D-glucofuranose (11). Crude ester **11** was obtained in quantitative yield on an 11-mmol scale and purified by high-pressure LC with elution with 15% ether in hexanes which gave 2.19 g (65%) of pure ester

11: IR (film) 1745, 1380, 1370, 1210, 1160, 1080, 1070, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3 H, t, J = 8), 1.32 (6 H, s), 1.40 (3 H, s), 1.52 (3 H, s), 2.37 (2 H, q, J = 8), 4.45 (1 H, d, J = 4), 5.25 (1 H, d, J = 2), 5.85 (1 H, d, J = 4). Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.96; H, 7.65. Found: C, 57.24; H, 7.62.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-propionyl-α-D-galactopyranose (12). Crude ester 12 was obtained in 97% yield on a 10-mmol scale. The product was purified by chromatography on silica gel eluted with 30% ether in hexanes which gave 2.4 g (76%) of pure 12: IR (thin film) 1740, 1380, 1370, 1260, 1070, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (3 H, t, J = 8), 1.37 (6 H, s), 1.45 (3 H, s), 1.52 (3 H, s), 2.35 (2 H, q, J = 8), 4.60 (1 H, dd, J = 7, 4), 5.48 (1 H, d, J = 4). Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 56.92; H, 7.61.

2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl Propionate (13). Crude ester 13 was obtained in quantitative yield on a 10-mmol scale. It was purified by chromatography on silica gel eluted with 30% ether in hexanes which gave 2.2 g (70%) of pure ester 13. When pure, ester 13 crystallizes slowly: mp 42–44 °C; IR (thin film) 1750, 1380, 1370, 1210, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (3 H, t, J = 8), 1.33 (3 H, s), 1.37 (3 H, s), 1.47 (3 H, s), 1.48 (3 H, s), 2.32 (2 H, q, J = 8), 6.06 (1 H, br s). Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.96; H, 7.65. Found: C, 56.95; H, 7.66.

Methyl 4,5-*O*-Isopropylidene-2-*O*-propionyl-β-D-arabinopyranoside (14). Crude ester 14 was obtained in 86% yield on an 8.8-mmol scale. It was purified by recrystallization from hexanes which gave 1.5 g (66%) of pure ester 14: mp 83–85 °C; IR (1% in $CHCl_3$) 1740, 1380, 1370, 1360, 1170, 1130, 1090, 1060, 910, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (3 H, t, J = 8), 1.37 (3 H, s), 1.55 (3 H, s), 2.40 (2 H, q, J = 8), 3.40 (3 H, s). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.44; H, 7.76.

1,2:4,5-Di-*O*-isopropylidene-3-*O*-propionyl-β-D-fructopyranose (15). Crude ester 15 was obtained in 90% yield on a 7.8-mmol scale. It was purified by chromatography on silica gel eluted with 60% ether in hexanes which gave 1.72 g (70%) of pure 15 as a thick colorless oil: IR (thin film) 1740, 1380, 1370, 1220, 1190, 1170, 1080, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (3 H, t, J = 7.5), 1.37 (3 H, s), 1.40 (3 H, s), 1.48 (3 H, s), 1.57 (3 H, s), 2.42 (2 H, q, J = 7.5), 5.10 (1 H, d, J = 7); ^{13}C NMR ($CDCl_3$) δ 8.9, 26.0, 26.2, 27.4, 27.6, 60.4, 71.7, 73.6, 74.8, 103.7, 109.4, 111.8, 173.7. Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 56.88; H, 7.54.

General Procedure for Aldol Condensations. Reactions of Ketone 4 with Benzaldehyde. To a solution of 0.25 mL (1.8 mmol) of diisopropylamine in 10 mL of dry THF at 0 °C was added 1.2 mL (1.8 mmol) of a 1.55 M solution of *n*-butyllithium in hexane. After 10 min the solution was cooled to −70 °C, and 0.50 g (1.6 mmol) of ketone 4 in 4 mL of THF was added at a rate such that the temperature remained below −65 °C. After the mixture was stirred for 30 min at −70 °C, 0.18 mL (1.8 mmol) of benzaldehyde was added, and the mixture was stirred for an additional 5 min and then quenched with 10 mL of saturated $NaHCO_3$. After warming to room temperature, the reaction mixture was extracted two times with ether. The ether layers were combined, dried (Na_2SO_4), and evaporated to give 620 mg (94%) of a yellow oil. The crude product was determined to be a 1.44:1.37:1.0 mixture of three aldols as determined by analytical high-pressure LC (15% ether/hexanes). A portion (580 mg) of the crude product was purified by preparative high-pressure LC to give 134 mg (22%) of an erythro aldol: mp 106–109 °C; IR (3% in $CHCl_3$) 3550, 1705, 1455, 1390, 1380, 1165, 1080, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (3 H, d, J = 7), 1.33 (3 H, s), 1.46 (3 H, s), 3.1 (1 H, m), 4.28 (1 H, d, J = 4), 5.02 (1 H, d, J = 2), 6.02 (1 H, d, J = 4), 7.13 (5 H, br s), 7.28 (5 H, br s); ^{13}C NMR ($CDCl_3$) δ 8.0, 26.3, 26.8, 49.4, 71.5, 72.7, 81.4, 84.5, 106.1, 112.4, 213.6; mass spectrum, m/e 394 ($M^+ - H_2O$, 0.04), 291 (0.56), 249 (2.46), 248 (1.98), 191 (1.01), 129 (0.89); m/e 394.1776 (calcd for $C_{24}H_{26}O_5$ ($M^+ - H_2O$), 394.1780). For the other erythro aldol: 108 mg (16%); IR ($CHCl_3$) 3550, 1705, 1450, 1385, 1375, 1160, 1080, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 7), 1.32 (3 H, s), 1.45 (3 H, s), 3.33 (1 H, m), 4.30 (1 H, d, J = 4), 4.68 (1 H, d, J = 4), 5.12 (1 H, d, J = 3), 6.00 (1 H, d, J = 4), 7.2 (10 H, br s); ^{13}C NMR ($CDCl_3$) δ 8.1, 26.2, 26.8, 49.1, 71.9, 72.6, 81.7, 83.8, 85.4, 105.8, 112.3, 211.7; mass spectrum, m/e 394 (0.03), 291 (0.20), 249 (1.79), 248 (0.09), 191 (0.51), 129 (0.50); m/e 394.1772 (calcd for $C_{24}H_{26}O_5$ ($M^+ - H_2O$), 394.1780). A threo aldol was also obtained: 112 mg (18%); IR ($CDCl_3$) 3500, 1705, 1455, 1385, 1375, 1165, 1080, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (3 H, d, J = 7), 1.32 (3 H, s), 1.46 (3 H, s), 3.1 (1 H, m), 3.70 (1 H, d, J = 4), 4.63 (1 H, d, J = 2), 4.83 (1 H, d, J = 4), 6.03 (1 H, d, J = 4), 7.3 (10 H, br s); ^{13}C NMR ($CDCl_3$) δ 13.6, 26.3, 26.9, 50.4, 72.7, 76.5, 81.5, 83.8, 85.9, 105.7, 112.2, 210.6; mass spectrum, m/e 394 (0.01), 291 (0.36), 249 (1.94), 248 (0.92), 191 (0.57), 129 (0.51); m/e 394.1768 (calcd for $C_{24}H_{26}O_5$ ($M^+ - H_2O$), 394.1780).

Reaction of Ketone 5 with Benzaldehyde. A crude mixture of aldols was obtained in quantitative yield on a 1.7-mmol scale. The crude product was determined to be a 63:37 mixture of two erythro isomers by ^1H NMR and ^{13}C NMR: ^1H NMR ($CDCl_3$) δ 1.1 (3 H, d, J = 7), 1.2 (3 H, d, J = 7), 5.3 (1 H, d, J = 4), 5.4 (1 H, d, J = 4), 7.3 (5 H, br s); ^{13}C NMR ($CDCl_3$) δ 9.7 (minor), 9.9, 18.3, 25.2, 26.6, 28.5, 47.7 (minor), 48.2, 59.7, 72.2, 72.6 (minor), 73.4, 86.3 (minor), 86.5, 97.2, 113.6, 126.0, 126.6, 127.6, 206.4, 207.6. Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.12. Found: C, 64.62; H, 7.14.

Reaction of Ketone 6 with Benzaldehyde. The crude mixture of aldols was obtained in 96% yield on a 1.9-mmol scale. The crude product was a 4:1 mixture of two erythro aldols as determined by ^{13}C NMR, ^1H NMR, and analytical high-pressure LC (15% ether/hexanes). The mixture from a 7.0-mmol preparation was separated by using high-pressure LC with elution with 20% ether in hexanes.

Aldol 35 was obtained in 15% yield as white crystals: mp 105–107 °C; $[\alpha]_D$ −18.6 (c 1.48, acetone); CD (c 0.0144, cyclohexane; 22 °C) $[\Theta]_{340}$ 0, $[\Theta]_{315}$ −2500, $[\Theta]_{240}$ 0; IR (1% in $CHCl_3$) 3500, 1708, 1390, 1380, 1250, 1170, 1160, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (3 H, d, J = 7), 1.37 (6 H, br s), 1.43 (3 H, s), 1.52 (3 H, s), 3.5 (1 H, dd, J = 7, 2), 5.11 (1 H, d, J = 2), 7.26 (5 H, br s); ^{13}C NMR ($CDCl_3$) δ 208.4, 141.7, 127.8, 126.9, 125.9, 109.7, 108.9, 101.8, 72.3, 70.3, 70.1, 70.0, 61.4, 46.7, 25.9, 24.5, 23.9, 9.7. Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.52; H, 7.02.

Aldol 34 was obtained in 55% yield as crystals: mp 82–84 °C; $[\alpha]_D$ −84.2 (c 1.52, acetone); CD (c 0.0144, cyclohexane; 22 °C) $[\Theta]_{300}$ +8900, $[\Theta]_{340}$ 0; IR (1% in $CHCl_3$) 3500, 1715, 1460, 1385, 1375, 1260, 1220, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (3 H, d, J = 7), 1.15 (3 H, s), 1.32 (3 H, s), 1.36 (3 H, s), 1.50 (3 H, s), 5.15 (1 H, d, J = 4); ^{13}C NMR ($CDCl_3$) δ 206.3, 142.1, 127.8, 126.9, 126.2, 109.5, 108.8, 101.7, 72.9, 70.1, 70.0, 61.3, 47.5, 25.8, 25.7, 24.2, 23.9, 10.6. Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.24; H, 7.19. Found: C, 64.56; H, 7.21.

Reaction of Ketone 7 with Benzaldehyde. The crude aldol was obtained in 93% yield on a 1.8-mmol scale and was determined to be a 1:1 mixture of diastereomers by ^{13}C NMR. The crude product was purified by chromatography on silica gel (30% ether in hexanes) to yield the aldols as a colorless oil (65%): ^1H NMR ($CDCl_3$) δ 1.42 (6 H, br s), 1.46 (3 H, s), 1.57 (3 H, s), 3.20 (3 H, d, J = 6), 5.17 (1 H, t, J = 6), 7.33 (5 H, br s); ^{13}C NMR ($CDCl_3$) δ 203.6, 143.1, 128.1, 127.2, 125.6, 109.6, 108.9, 108.8, 101.4, 70.3, 70.2, 70.0, 69.8, 69.2, 61.2, 46.3, 46.0, 25.8, 24.4, 23.9. Anal. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93. Found: C, 63.66; H, 7.48.

Reaction of Ketone 8 with Benzaldehyde. The crude aldols were obtained in quantitative yield on a 13-mmol scale. The mixture was determined to contain four aldol products. The two major products were erythro aldols representing 60% and 35% of the mixture. The two threo isomers, which were not separated, totaled 5% of the mixture. The major erythro aldol was separated by high-pressure LC with elution with 20% ether in hexanes. The minor erythro aldol was contaminated with the threo aldols.

Aldol 38 was obtained in 26% yield as a thick colorless oil: R_f (20% ether in hexanes) 0.22; IR (thin film) 3500, 1705, 1450, 1380, 1370, 1260, 1250, 1220, 1210, 1160 (br), 1110, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.13 (9 H, s), 0.93 (3 H, d, J = 7), 1.33 (3 H, s), 1.43 (3 H, s), 1.50 (3 H, s), 1.57 (3 H, s), 5.1 (1 H, d, J = 2.5), 7.1–7.4 (5 H, m); ^{13}C NMR ($CDCl_3$) δ −0.10, 10.2, 24.2, 25.6, 25.9, 26.6, 47.5, 61.4, 70.1, 70.4, 70.9, 79.3, 103.5, 109.3, 126.0, 126.8, 127.9, 142.2, 213.7. Anal. Calcd for $C_{25}H_{38}O_8Si$: C, 60.70; H, 7.74. Found: C, 60.52; H, 7.74.

Aldol 39 (including the threo contaminant) was obtained in 21% yield as a thick colorless oil: R_f 0.26; IR (thin film) 3510, 1705, 1450, 1380, 1370, 1250, 1220, 1160, 1105, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.17 (9 H, s), 0.92 (3 H, d, J = 7), 1.33 (3 H, s), 1.41 (3 H, s), 1.44 (3 H, s), 1.48 (3 H, s), 5.1 (1 H, d, J = 2), 7.24 (5 H, br s); ^{13}C NMR ($CDCl_3$) δ −0.15, 9.3, 24.0, 25.9, 26.4, 49.0, 61.3,

70.1, 70.4, 70.7, 71.8, 77.6, 103.9, 109.0, 125.7, 126.7, 127.9, 142.0, 214.2. Anal. Calcd for $C_{25}H_{38}O_8Si$: C, 60.70; H, 7.74. Found: C, 60.36; H, 7.78.

(-)-Methyl *erythro*-3-Hydroxy-2-methyl-3-phenylpropanoate (41). To a stirred solution of 4.8 g (21 mmol) of H_5IO_6 in 15 mL of H_2O was added 1.06 g (2.1 mmol) of aldol **38** in 25 mL of methanol. After being stirred for 40 h, the reaction mixture was concentrated in vacuo, and the residue was extracted three times with CH_2Cl_2. The CH_2Cl_2 layers were combined, dried ($MgSO_4$), and evaporated to give 0.73 g (>100%) of **40** as an orange oil. The crude acid was treated with an ether solution of diazomethane. After evaporation of the solvent, the residue was chromatographed on silica gel (40% ether/hexanes) to give 0.175 g (43%) of **41** as a colorless oil, $[\alpha]^{20}_D$ -19.3 (*c* 1.74, $CHCl_3$). The compound was identical by ^1H NMR with an authentic sample of the racemic ester.[5]

(+)-Methyl *erythro*-3-Hydroxy-2-methyl-3-phenylpropanoate (44). In a procedure identical with that used for the (-) enantiomer, the second high-pressure LC fraction was cleaved with H_5IO_6 and treated with diazomethane. The erythro ester **44** was obtained pure by chromatography on silica gel (40% ether/hexanes); $[\alpha]^{20}_D$ +21.5 (*c* 1.73, $CHCl_3$). The threo ester was also obtained. This material was identical by ^1H NMR with an authentic sample of racemic threo ester;[5] $[\alpha]^{20}_D$ +6.89 (*c* 1.48, $CHCl_3$) (lit.[28,29] (optically pure threo ester) $[\alpha]^{20}_D$ -57.1). The threo ester obtained is therefore a 60:40 mixture of enantiomers resulting from a 60:40 mixture of initial aldols.

(-)-*erythro*-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (40). Methyl ester **41** (0.15 g, 0.77 mmol) was treated with a solution of 0.44 g (7.7 mmol) of KOH in 5 mL of 4:1 methanol-water at room temperature for 3 h. The reaction mixture was acidified with 10% HCl and extracted three times with CH_2Cl_2. The CH_2Cl_2 layers were combined, dried ($MgSO_4$), and evaporated to give 0.11 g (74%) of acid **40** as a white crystalline solid: mp 85–87 °C; $[\alpha]^{20}_D$ -29.5 (*c* 2.03, $CHCl_3$). This compound is identical by ^1H NMR with authentic racemic erythro acid.[5]

(+)-*erythro*-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (43). Methyl ester **44** was saponified as described above to give a 72% yield of **43** as a white crystalline solid: mp 87–88 °C; $[\alpha]^{20}_D$ +29.5 (*c* 1.27, $CHCl_3$). This compound is identical by ^1H NMR with authentic racemic erythro acid.[5]

Reaction of Ester 9 with Benzaldehyde. The crude aldol product was obtained in 100% yield on a 1.7-mmol scale. The crude product was determined to be a mixture of a threo and two erythro isomers in a 3:1:1 ratio by ^{13}C NMR and analytical high-pressure LC: ^1H NMR ($CDCl_3$) δ 1.0–1.2 (methyl doublets), 1.2–1.6 (methyl singlets), 4.8 (1 H, d, J = 9), 5.1 (1 H, d, J = 4), 5.2 (1 H, d, J = 4), 7.33 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 10.5, 11.0, 14.0, 24.0, 25.1, 25.7, 26.2, 26.7, 46.5, 47.0, 47.4, 61.2, 65.3, 65.6, 70.0, 70.3, 70.7, 73.2, 73.8, 76.0, 76.2, 101.3, 108.5, 109.0, 125.8, 126.5, 126.6, 127.2, 127.8, 128.2, 141.7, 174.7. Anal. Calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16. Found: C, 62.93; H, 7.25.

Reaction of Ester 11 with Benzaldehyde. The crude aldol product was obtained in 99% yield on a 1.7-mmol scale. The crude product was determined to be a mixture of all four possible aldol isomers, two threo isomers and two erythro isomers in a 3.3:2.4:3.3:1 ratio by ^{13}C NMR. An analytical sample of this mixture was obtained by chromatography on silica gel eluted with 40% ether in hexanes: ^1H NMR ($CDCl_3$) δ 0.9–1.2 (methyl doublets), 1.2–1.6 (methyl singlets), 7.4 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 10.7, 11.9, 13.5, 13.9, 24.8, 25.9, 26.4, 47.0, 47.4, 47.5, 66.8, 67.0, 67.1, 72.4, 72.6, 75.9, 79.8, 83.0, 104.9, 111.9, 125.9, 126.4, 127.2, 127.6, 127.9, 128.1, 141.5, 172.8. Anal. Calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16. Found: C, 62.68; H, 7.26.

Reaction of Ester 10 with Benzaldehyde. The crude aldol product was obtained in 100% yield on a 1.7-mmol scale. The crude product was determined to be a mixture of all four possible aldols, two threo isomers and two erythro isomers in a 3.8:2.2:1.6:1 ratio by ^{13}C NMR. An analytical sample was prepared by chromatography on silica gel eluted with 35% ether in hexanes: ^1H NMR ($CDCl_3$) δ 1.00 (methyl, d, J = 7), 1.02 (methyl, d, J = 7), 1.16 (methyl, d, J = 7), 1.30 (methyl, s), 1.63 (methyl, s), 7.27 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 11.6, 11.8, 14.2, 14.6, 20.0, 21.8, 22.0, 23.1, 24.9, 26.2, 26.4, 26.9, 47.3, 47.8, 60.3, 69.9, 70.2, 73.2, 76.0, 76.1, 83.7, 106.4, 107.6, 108.3, 126.0, 126.3, 126.4, 127.2, 127.6, 128.0, 128.2, 142.1, 174.2, 174.4. Anal. Calcd for $C_{24}H_{34}O_5$: C, 63.98; H, 7.61. Found: C, 63.90; H, 7.57.

Reaction of Ester 12 with Benzaldehyde. The aldol product was obtained pure in 90% yield on a 1.7-mmol scale. The crude product was determined to be a mixture of all four possible aldols, two threo isomers and two erythro isomers in a 3.6:3.5:1.6:1 ratio by ^{13}C NMR and analytical high-pressure LC (30% ether/hexanes): ^1H NMR ($CDCl_3$) δ 0.9–1.2 (methyl doublets), 1.2–1.6 (methyl singlets), 3.0 (1 H, m), 5.1 (benzylic H, d, J = 3), 5.3 (benzylic H, d, J = 3), 5.6 (1 H, d, J = 5), 7.3 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 9.7, 10.7, 14.0, 14.1, 24.2, 24.6, 25.7, 46.6, 47.5, 47.6, 63.0, 63.3, 65.5, 65.8, 70.3, 70.6, 73.1, 73.4, 75.9, 76.1, 96.0, 108.5, 109.4, 125.7, 126.5, 126.9, 127.0, 127.2, 127.6, 127.8, 127.9, 128.1, 141.6, 141.8, 175.0. Anal. Calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16. Found: C, 62.68; H, 7.28.

Reaction of Ester 13 with Benzaldehyde. The aldol product was obtained pure in 90% yield on a 1.7-mmol scale. The crude product was determined to be a mixture of all four possible aldols, two threo isomers and two erythro isomers in a 2.8:2.4:1.7:1 ratio by ^{13}C NMR: ^1H NMR ($CDCl_3$) δ 0.9–1.2 (methyl doublets), 1.2–1.6 (methyl singlets), 7.3 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 10.1, 10.6, 12.2, 12.5, 23.0, 23.5, 24.2, 25.2, 45.4, 45.7, 65.0, 71.2, 71.7, 72.4, 74.5, 77.6, 78.1, 78.6, 80.0, 83.4, 84.1, 99.5, 107.6, 111.5, 124.6, 125.1, 125.7, 126.1, 126.4, 126.7, 126.8, 140.1, 140.3, 171.8, 172.3. Anal. Calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16. Found: C, 62.48; H, 7.18.

Reaction of Ester 14 with Benzaldehyde. The aldol product was obtained pure in 100% yield on a 1.7-mmol scale. The crude product was determined to be a mixture of all four possible aldol products, two threo isomers and two erythro isomers in an 11:9.2:2.2:1 ratio by ^{13}C NMR: ^1H NMR ($CDCl_3$) δ 1.10 (3 H, s, J = 8), 1.3 (3 H, s), 1.5 (3 H, s), 2.9 (1 H, m), 3.35 (3 H, br s), 3.9 (2 H, br s), 4.2 (2 H, m), 4.9 (3 H, m), 7.3 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 10.3, 11.1, 13.5, 13.7, 25.9, 27.5, 46.5, 46.8, 47.4, 55.2, 58.3, 58.4, 71.7, 71.9, 72.5, 73.1, 75.7, 76.0, 96.7, 96.9, 109.1, 126.5, 127.6, 127.8, 128.0, 141.2, 141.5, 174.3, 174.6. Anal. Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 62.17; H, 7.17.

Reaction of Ester 15 with Benzaldehyde. The crude aldol product was obtained in 86% yield on a 1.7-mmol scale. The crude product was determined to be a mixture of all four possible aldol products, two threo isomers and two erythro isomers in a 6:2:1:1 ratio by ^{13}C NMR. An analytical sample was prepared by chromatography on silica gel eluted with 60% ether in hexanes: ^1H NMR ($CDCl_3$) δ 1.0 (3 H, d, J = 7), 1.3 (3 H, s), 1.4 (3 H, s), 1.47 (3 H, s), 1.5 (3 H, s), 2.9 (1 H, m), 7.3 (5 H, s); ^{13}C NMR ($CDCl_3$) δ 9.8, 10.5, 13.6, 25.5, 25.9, 26.3, 27.3, 46.5, 47.0, 47.7, 59.9, 60.2, 69.8, 70.0, 71.0, 73.0, 73.4, 74.2, 74.4, 76.1, 103.3, 104.3, 108.7, 109.2, 111.3, 111.7, 126.4, 127.6, 127.8, 128.0, 141.3, 141.6, 174.1, 174.8. Anal. Calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16. Found: C, 62.29; H, 7.34.

Reaction of Ketone 6 with (*R*)-Glyceraldehyde Acetonide (46). The crude mixture of **50**, **51**, and a threo aldol was obtained in 94% yield on a 1.7-mmol scale. The crude product was determined to be a mixture of three aldol products, two erythro isomers and one threo isomer in a ratio of 5.5:2.5:1. Analysis was done on the mixture. Anal. Calcd for $C_{20}H_{32}O_9$: C, 57.68; H, 7.74. Found: C, 57.85; H, 7.80. The mixture was chromatographed on silica gel (1:1 ether–hexanes). A small amount of the two major isomers could be obtained pure, with the remainder being a mixture. Aldol **50**: $[\alpha]^{24}_D$ -40 (*c* 1.4, $CHCl_3$); CD (*c* 0.36, cyclohexane; 22 °C) $[\Theta]_{345}$ 0, $[\Theta]_{320}$ +460, $[\Theta]_{265}$ 0; ^{13}C NMR ($CDCl_3$) δ 205.6, 109.8, 109.4, 108.9, 101.5, 71.2, 70.1, 69.9, 66.3, 61.4, 44.2, 26.4, 26.1, 25.8, 25.3, 24.6, 23.9, 12.6. Aldol **51**: $[\alpha]_D$ -22 (*c* 0.9, $CHCl_3$); CD (*c* 0.40, cyclohexane; 22 °C) $[\Theta]_{340}$ 0, $[\Theta]_{297}$ +4000, $[\Theta]_{250}$ 0; ^{13}C NMR ($CDCl_3$) δ 208, 109.1, 108.9, 101.5, 75.0, 72.1, 70.3, 70.2, 69.9, 61.4, 41.7, 26.6, 25.2, 24.6, 24.0, 10.7.

Reaction of Ketone 6 with (*S*)-Glyceraldehyde Acetonide (47). Formation of Aldol 52. Crude aldol **52** was obtained in 90% yield on a 1.7-mmol scale. The crude product was determined to be a single aldol by ^{13}C NMR. The crude product was chromatographed on silica gel (1:1 ether–hexanes) to give pure **52** in 82% yield as a colorless oil: $[\alpha]^{24}_D$ -58.7 (*c* 1.04, $CHCl_3$); CD (*c*

(28) T. Matsumoto, I. Tanaka, and K. Fukui, *Bull. Chem. Soc. Jpn.*, 44, 3378 (1971).
(29) J. Canciell, J. Gabard, and J. Jacques, *Bull. Soc. Chim. Fr.*, 231 (1968).

0.019, cyclohexane; 22 °C) $[\Theta]_{340}$ 0, $[\Theta]_{300}$ +3250, $[\Theta]_{240}$ 0; IR (thin film) 3500, 1725, 1380, 1370, 1250, 1210, 1070, 990, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (3 H, d, J = 7), 1.33 (9 H, br s), 1.40 (3 H, s), 1.43 (3 H, s), 1.52 (3 H, s), 3.5 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 206.9, 109.7, 108.9, 101.7, 75.7, 71.5, 70.2, 70.0, 66.3, 61.9, 42.4, 26.6, 26.0, 25.8, 25.2, 24.6, 24.0, 10.5. Anal. Calcd for $C_{20}H_{32}O_9$: C, 57.68; H, 7.74. Found: C, 57.91; H, 7.93.

Reaction of Ketone 5 with (*R*)-Glyceraldehyde Acetonide (46). The crude mixture of aldols was obtained in 95% yield on a 1.7-mmol scale. The crude product was determined to be a mixture of three aldol products by ^{13}C NMR in a ratio of 2.5:2.3:1. TLC (35% ether in hexanes, developed with H_2SO_4) showed three overlapping spots: R_f 0.22, 0.17, 0.12. By ^{13}C NMR the two major products were determined to be erythro. The crude product was purified by chromatography on silica gel eluted with 50% ether in hexanes to give the three aldol products in 63% yield as a thick, colorless oil: ^1H NMR ($CDCl_3$) δ 1.0–1.6 (methyl singlets and doublets), 3.9–4.8 (complex multiplets of H's α to oxygens); ^{13}C NMR ($CDCl_3$) δ 11.5 (both erythro), 14.5 (threo), 18.4, 19.0, 24.9, 25.2, 25.5, 26.0, 26.3, 26.7, 26.8, 28.6, 42.6 (erythro), 43.5 (threo), 44.6 (erythro), 59.7, 59.9, 66.0, 70.7, 71.9, 72.1, 72.5, 73.5, 75.6, 77.3, 85.5, 86.1, 86.6, 86.9, 97.2, 108.7, 109.1, 113.0, 113.4, 114.0, 206.1. Anal. Calcd for $C_{20}H_{32}O_9$: C, 57.68; H, 7.74. Found: C, 57.82; H, 7.67.

Reaction of Ketone 5 with (*S*)-Glyceraldehyde Acetonide (47). The crude mixture of aldols was obtained in 94% yield on a 1.7-mmol scale. The crude product was analyzed by ^{13}C NMR and found to be a mixture of three aldol products in a ratio of 7:1:1. The major aldol is erythro, and the two minor products are erythro and threo. The crude product was purified by chromatography on silica gel eluted with 50% ether in hexanes. All fractions containing aldol product were combined to give a 50% yield of a very thick, colorless oil: ^1H NMR ($CDCl_3$) δ 1.0–1.6 (methyl singlets and doublets), 3.9–4.8 (complex multiplets of hydrogens α to oxygen); ^{13}C NMR ($CDCl_3$) δ 10.7 (major erythro), 12.4 (minor erythro), 14.2 (threo), 18.4, 25.0, 25.5, 26.4, 26.7, 28.5, 43.1 (major erythro), 44.1 (minor), 44.6 (minor), 59.7, 59.8, 66.0, 71.3, 72.3, 72.5, 73.4, 73.6, 75.7, 86.3, 86.6, 97.2, 108.8, 113.0, 113.4, 113.6, 206.5. Anal. Calcd for $C_{20}H_{32}O_9$: C, 57.68; H, 7.74. Found: C, 57.74; H, 7.73.

Reaction of Ketone 7 with (*R*)-Glyceraldehyde Acetonide (46). Crude aldols **58** and **59** were obtained in 92% yield on a 1.8-mmol scale. The product was determined to be a 1.8:1 mixture of **58** and **59** by ^{13}C NMR. The crude product was purified by chromatography on silica gel (60% ether–hexanes) to give **58** and **59** in 63% yield as a thick, colorless oil: ^1H NMR ($CDCl_3$) δ 1.2–1.8 (methyl singlets), 2.8–3.2 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 23.9, 24.5, 25.0, 25.8, 26.2, 26.4, 40.8 (minor), 41.0 (major), 61.3, 65.4 (minor), 66.4 (major), 67.2 (minor), 68.2 (major), 69.8, 70.1, 70.4, 77.6, 77.9, 101.4, 108.9, 109.1, 109.2, 109.8, 203.2 (minor), 204.3 (major). Anal. Calcd for $C_{19}H_{30}O_9$: C, 56.71; H, 7.51. Found: C, 56.82; H, 7.60.

Reaction of Ketone 7 with (*S*)-Glyceraldehyde Acetonide (47). Crude aldols **60** and **61** were obtained in 90% yield on a 1.8-mmol scale. The product was determined to be a 1.6:1 mixture of **60** and **61** by ^{13}C NMR. The crude product was purified by chromatography on silica gel (2:1, ether–hexanes) to give **60** and **61** in 30% yield as a colorless oil: IR (thin film) 3500, 1730, 1380, 1370, 1250, 1210, 1070, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2–1.8 (methyl singlets), 2.8–3.2 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 24.0, 24.6, 25.2, 25.3, 25.5, 25.9, 26.3, 26.5, 40.8 (minor), 41.1 (major), 61.4, 65.5 (minor), 66.5 (major), 67.2 (minor), 68.5 (major), 69.9, 70.2, 70.5, 77.7, 101.4, 108.9, 109.0, 109.3, 109.6, 109.9, 203.4 (minor), 204.3 (major). Anal. Calcd for $C_{19}H_{30}O_9$: C, 56.71; H, 7.51. Found: C, 56.76; H, 7.52.

General Procedure for Aldol Condensations in Tetramethoxybutane. To a solution of 0.20 mL (1.2 mmol) of 2,2,6,6-tetramethylpiperidine in 3 mL of TMB and 1 mL of pentane at −20 °C was added 0.80 mL (1.2 mmol) of 1.5 M *n*-butyllithium in hexane. After 5 min the solution was cooled to −70 °C, and 1.0 mmol of the ketone in 1 mL of pentane was added dropwise. After the mixture was stirred for 1 h at −70 °C, 1.0 mmol of the ketone was added, and the mixture was stirred 1–5 min and quenched with 4 mL of saturated $NaHCO_3$. After warming to room temperature, the reaction mixture was extracted two times with ether. The ether layers were combined, dried ($CaCl_2$), and evaporated to give a residue which contained the aldol plus TMB. The TMB was removed by evacuation at 5 × 10^{-3} torr overnight (16 h). Purification, if necessary, was performed as described before. Results are summarized in Tables III and IV.

Crystal Structure of Aldol 34. Crystallographic Data Collection. A $C_{21}H_{28}O_7$ crystal with approximate dimensions 0.8 × 0.2 × 0.2 mm was mounted on a glass fiber with epoxy cement such that the longest crystal dimension was approximately parallel to the fiber axis.

Unit cell parameters and the orientation matrix were determined on a Syntex $P2_1$ four-circle diffractometer equipped with a graphite monochromator (Bragg 2θ angle 12.2°) by using Mo Kα radiation at a takeoff angle of 6.75°. Fifteen reflections whose 2θ values ranged from 6.04° to 19.75° were machine centered and used in least-squares refinement of the lattice parameters and orientation matrix. The unit cell parameters obtained were a = 11.04 (1) Å,[30] b = 0.438 (5) Å, c = 11.63 (1) Å, β = 105.16 (7)°, V = 1046 (1) Å^3. The calculated density of 1.246 g cm^{-3} for two formula units per cell agrees with the experimental density of 1.240 g cm^{-3} measured by the flotation method using a mixture of $ZnCl_2$ and H_2O. ω scans of several low 2θ angle reflections gave peak widths at half-height of less than 0.24°, indicating a satisfactory mosaic spread for the crystal.

Axial photographs indicated that the crystal belonged to the monoclinic system. Intensity data for zero and upper levels were collected at a rapid scan rate and the intensities examined carefully for systematic absences. The absence of $0k0$ ($k = 2n + 1$) is consistent with either space group $P2_1$ or $P2_1/m$ (No. 4 or 11).[31] Our initial choice of $P2_1$ was confirmed by successful refinement in that space group.

Intensity data were collected by using θ–2θ scans with the X-ray source and monochromator settings identical with those used for determination of the unit cell parameters. A variable scan rate of from 2.93° to 29.30°/min was used, and a scan width of 2.0° was sufficient to collect all of the peak intensity. Stationary background counts were measured at the beginning (bgd1) and at the end (bgd2) of each scan with a total background to scan time ratio, TR, of 1.0. No significant fluctuations were observed in the intensities of three standard reflections (005; 500; 040) monitored every 97 reflections. Intensities were calculated from the total scan count (CT) and background counts by the relationship I = CT − (TR)(bgd1 + bgd2). The intensities and structure factors were assigned standard deviations according to eq 9 from a total of 1991 reflections collected in a complete

$$\sigma(I) = [\mathrm{CT} + (\mathrm{TR})^2(\mathrm{bgd1} + \mathrm{bgd2})] \quad (9a)$$

$$\sigma(F) = \sigma(I)/(2F)\mathrm{Lp} \quad (9b)$$

quadrant of data out to 2θ = 50°; 1619 were accepted as statistically above background on the basis that F was greater than $3\sigma(F)$. Lorentz and polarization corrections were made in the usual way.

Solution and Refinement of the Structure. Computations were performed by using standard programs;[32] all computations were carried out on the CDC Cyber 74 system. For structure factor calculations the scattering factors were taken from Cromer and Waber's tabulation.[33] The scattering factor(s) for all atoms except hydrogen was corrected for the real and imaginary anomalous dispersion components.[33] The agreement factors are defined in the usual way as in eq 10 and 11. In all least-squares refinements,

$$R = (\sum||F_o| - |F_c||)/(\sum|F_o|) \quad (10)$$

$$R_w = [\sum(|F_o| - |F_c|)w^{1/2}/\sum(|F_o|)w^{1/2}] \quad (11)$$

the quantity minimized was $\sum(|F_o| - |F_c|)^2$. A weighting scheme based on counting statistics ($w = 2.6/(\sigma(F)^2 + 0.0004F^2)$ was

(30) Numbers in parentheses here and in the tables indicate estimated standard deviations in the least significant digit(s).

(31) "International Tables for X-Ray Crystallography", Vol. I, Kynoch Press, Birmingham, England, 1952.

(32) Programs utilized were Sheldrich's SHELX-76 program, Johnson's ORTEP program, Main, Germain, and Woolfoon's MULTAN, and Zalkin's FORDAP.

(33) "International Tables for X-Ray Crystallography", Vol. IV, Kynoch Press, Birmingham, England, 1974, pp 99–101, 149–150.

employed for calculation of R_w and in least-squares refinement.

The structure was solved by using MULTAN. The E map contained the positions for 21 of the nonhydrogen atoms. The other nonhydrogen atoms and the hydroxy hydrogen were located from Fourier syntheses. The remaining hydrogen positions were calculated by using the riding option in SHELX-76. A total of 176 parameters was varied and included a scale factor, positional parameters for oxygen and carbon, anisotropic thermal parameters for the oxygens, and isotropic thermal parameters for the remaining atoms. The final R was 0.072, and R_w = 0.072.

Final positional and thermal parameters are given in Tables VI and VII. A list of calculated and observed structure factors is available.[34]

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Registry No. 4, 50693-03-3; 4 (aldol isomer 1), 71748-73-7; 4 (aldol isomer 2), 71699-76-8; 4 (aldol isomer 3), 76581-91-4; 5, 76498-36-7; 5 (aldol isomer 1), 76514-43-7; 5 (aldol isomer 2), 76514-44-8; 6, 72519-57-4; 7, 76498-37-8; 7 (aldol isomer 1), 76498-38-9; 8, 76498-39-0; 8 (aldol isomer 1), 76498-40-3; 8 (aldol isomer 2), 76498-41-4; 9, 76498-42-5; 9 (aldol isomer 1), 76498-43-6; 9 (aldol isomer 2), 76548-83-9; 9 (aldol isomer 3), 76581-95-8; 10, 76498-44-7; 10 (aldol isomer 1), 76498-45-8; 10 (aldol isomer 2), 76548-84-0; 10 (aldol isomer 3), 76548-85-1; 10 (aldol isomer 4), 76548-86-2; 11, 76498-46-9; 11 (aldol isomer 1), 76498-47-0; 11 (aldol isomer 2), 76581-96-9; 11 (aldol isomer 3), 76548-87-3; 11 (aldol isomer 4), 76548-88-4; 12, 76498-48-1; 12 (aldol isomer 1), 76498-49-2; 12 (aldol isomer 2), 76548-89-5; 12 (aldol isomer 3), 76548-90-8; 12 (aldol isomer 4), 76548-91-9; 13, 76498-50-5; 13 (aldol isomer 1), 76498-51-6; 13 (aldol isomer 2), 76548-92-0; 13 (aldol isomer 3), 76548-93-1; 13 (aldol isomer 4), 76548-94-2; 14, 76498-52-7; 14 (aldol isomer 1), 76498-53-8; 14 (aldol isomer 2), 76548-95-3; 14 (aldol isomer 3), 76548-96-4; 14 (aldol isomer 4), 76548-97-5; 15, 76498-54-9; 15 (aldol isomer 1), 76498-55-0; 15 (aldol isomer 2), 76548-98-6; 15 (aldol isomer 3), 76548-99-7; 15 (aldol isomer 4), 76549-00-3; 16, 582-52-5; 16 (benzyl derivative), 18685-18-2; 17, 51306-24-2; 18, 18467-77-1; 19, 52507-90-1; 20, 20880-92-6; 20 (aldehyde oxidation product), 32786-02-0; 21, 76498-56-1; 22, 50767-73-2; 23, 76498-57-2; 24, 76498-58-3; 25, 76498-59-4; 26, 76498-60-7; 27, 4064-06-6; 28, 14131-84-1; 29, 38088-60-7; 30, 18422-54-3; 34, 72519-59-6; 35, 72581-18-1; 36/37, 76549-01-4; 38, 76498-61-8; 39, 76514-45-9; 40, 76549-02-5; 41, 76549-03-6; 43, 76549-04-7; 44 (isomer 1), 76549-05-8; 44 (isomer 2), 34880-62-1; 46, 15186-48-8; 47, 22323-80-4; 48, 76498-62-9; 49, 76498-63-0; 50, 72581-16-9; 51, 72581-15-8; 52, 72519-58-5; 53, 72581-17-0; 54, 76498-64-1; 55, 76498-65-2; 56, 76498-66-3; 57, 76549-06-9; 58, 76498-67-4; 59, 76549-07-0; 60, 76549-08-1; 61, 76549-09-2; 65, 72507-50-7; benzyl chloride, 100-44-7; aldehyde intermediate (Scheme I), 23558-05-6; potassium 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-2-hexulopyranosonate, 54162-42-4; (chloromethyl)trimethylsilane, 2344-80-1; 3-mercaptole acetal 1,2-dideoxy-5,6:7,8-di-*O*-isopropylidene-β-D-*arabino*-3,4,5-nonotriulo-5,9-pyranose, 76498-68-5; bis(trimethylsilyl)acetamide, 10416-58-7; propionyl chloride, 79-03-8; benzaldehyde, 100-52-7.

Supplementary Material Available: Tables of atomic coordinates and thermal parameters (Tables VI and VII), bond lengths (Table VIII), and bond angles (Table IX) (6 pages). Ordering information is given on any current masthead page.

(34) See the paragraph at the end of the paper regarding supplementary material.

Stereoselective Synthesis of Alcohols. 8. Diastereoselective Synthesis of β-Methylhomoallyl Alcohols via Crotylboronates[1,2]

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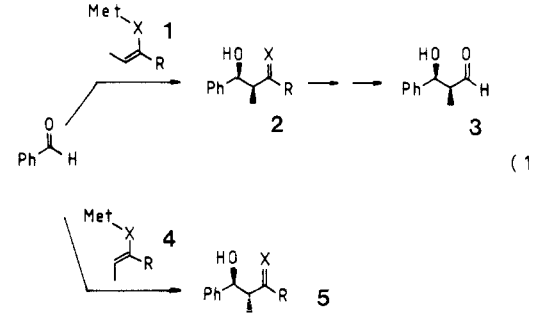
The (*E*)- and (*Z*)-butenylbis(dimethylamino)boranes **6c** and **8c** were obtained by starting from butenyl Grignard or butenylpotassium compounds. The aminoboranes were converted by pinacol to the crotylboronates **6d** and **8d**. These reagents have been added to various aldehydes, forming the homoallyl alcohols **15** and **16** with a diastereoselectivity of >95%.

Introduction

β-Methylalkanol units of both threo and erythro configuration[3] are a characteristic structural element of numerous macrolide[7] and polyether antibiotics. This caused interest in the development of new synthetic methods which allow the diastereoselective generation of β-methylalkanols.[8] Special attention has been given to those reactions in which new carbon–carbon bonds are formed via aldol addition, e.g., eq 1 (Met = Li, X = O).



In the aldol addition two prochiral components, the aldehyde and the enolate, are allowed to react. Hence, two diastereomeric products, the erythro adduct **2** and the threo adduct **5**[3] may result. This motivated the search for stereoselective synthetic methods which would lead to either the threo or the erythro isomer in high yield.[8] Thus it has been the aim of several investigations[8] to develop pairs of stereoisomeric reagents **1** and **4** which are capable of converting aldehydes stereoselectively to the adducts **2** and **5**, respectively. Useful reagents of this type should

(1) For paper VII, see R. W. Hoffmann and T. Herold, *Chem. Ber.*, **114**, 375 (1981).

(2) Portions of this work have been reported in preliminary form: R. W. Hoffmann and H. J. Zeiβ, *Angew. Chem.*, **91**, 329 (1979); *Angew. Chem., Int. Ed. Engl.*, **18**, 306 (1979).

(3) The terms erythro and threo are used in the sense defined by Heathcock[4] and Maskens.[5] This conforms to usage by most of the groups working on aldol-type additions. It should be made clear that this usage is contrary to the rules defined by *Chemical Abstracts* or *Beilstein*.[6]

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

(5) K. Maskens and N. Polgar, *J. Chem. Soc., Perkin Trans 1*, 109 (1973).

(6) *Beilstein, 4th ed.*, 4/1, XIV (1977); *Chem. Abst.*, **76**, Index Guide, 941 (1972).

(7) S. Masamune, G. S. Bates, and J. W. Corcoran, *Angew. Chem.*, **89**, 602 (1977); *Angew. Chem., Int. Ed. Engl.*, **16**, 585 (1977).

(8) Recently reviewed by P. A. Bartlett, *Tetrahedron*, **36**, 2 (1980).

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