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(17) The volume change $\Delta V$ associated with a high-spin–low-spin equilibrium in metMb·$N_3^-$ was estimated as ca. −15 mL/mol.



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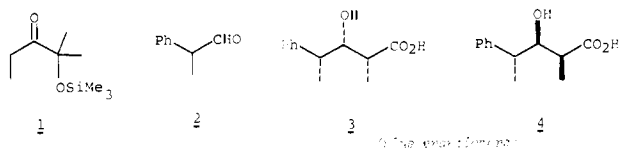
# Acyclic Stereoselection. 5. Use of Double Stereodifferentiation to Enhance 1,2 Diastereoselection in Aldol Condensations of Chiral Aldehydes[1]

*Sir:*

As we have previously demonstrated, successive aldol condensations can be used to synthesize complex polyketides such as the macrolide antibiotics, provided that sufficient stereochemical control can be achieved in the various steps.[2] The reagent that we have developed for this purpose (**1**) provides a highly stereoselective route to *erythro*-3-hydroxy-2-methylcarboxylic acids as long as the aldehyde substrate is achiral. However, when **1** is condensed with a chiral aldehyde such as

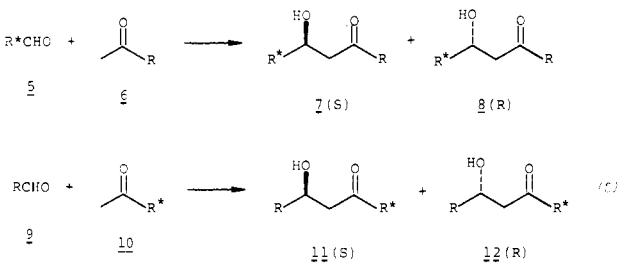


**1** **2** **3** **4**

**2**, two erythro products, resulting from attack of the reagent on the two diastereotopic faces of the aldehyde, are produced. After oxidation, erythro acids **3** and **4** are obtained in a ratio of 6:1. The 1,2 diastereoselectivity in the condensation of **1** with other $\alpha$-chiral aldehydes is in the range of 3:1 to 8:1, the major product being that predicted by Cram's empirical rule for 1,2 diastereoselection.[3] Although this particular erythro diastereomer is often the desired isomer for polyketide synthesis, the stereoselectivity is too low for a consecutive aldol strategy to be viable, since the overall stereochemical yield from such an approach is an exponential function of the average stereoselectivity of the various steps.

In principle, 1,2 diastereoselectivity can be enhanced by the use of "double stereodifferentiation".[4] We have examined the use of this little-appreciated strategy of stereoselective synthesis as a means of influencing the "Cram's rule selectivity" in aldol condensations of chiral aldehydes such as **2**. In this communication, we present the results of experiments which demonstrate the power of this method, and in the accompanying communication we report the synthesis of a new reagent (an analogue of **1**) which can be used for the stereoselective synthesis of $\beta$-hydroxy acids from chiral aldehydes.

The principle of double stereodifferentiation, as applied to the aldol condensation, may be illustrated as follows. In the reaction of a chiral aldehyde **5** with an achiral ketone **6**, diastereomers **7** and **8** are produced in unequal amounts (eq 1).



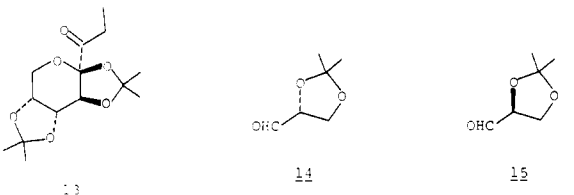
**5** **6** **7**(S) **8**(R)



**9** **10** **11**(S) **12**(R) (2)

As illustrated in eq 1, one enantiomer of **5** will yield **7** as the major product, and the other enantiomer will lead predominantly to **8**. Likewise, in the reaction of an achiral aldehyde **9** with a chiral ketone **10**, one enantiomer of **10** will yield primarily diastereomer **11**, while the other will afford diastereomer **12** as the major product (eq 2). Thus, we may visualize "*S*-selective" and "*R*-selective" enantiomers of both **5** and **10**, with regard to the chirality of the carbinol center created in an aldol condensation of either chiral reagent with an achiral partner. If we allow chiral aldehyde **5** to react with chiral ketone **10**, the *S*:*R* ratio will depend upon which pair of enantiomers are employed. It is intuitive that the relative amount of *S* configuration at the newly formed center will be greater when the two "*S*-selective" reactants combine than when *S*-selective **5** reacts with *R*-selective **10** or vice versa.

To examine this question, and to determine how much enhancement may be realized using such a ploy, we have utilized the enantiomerically homogeneous, chiral ketone **13** and the acetonides of the two enantiomers of glyceraldehyde (**14** and



**13** **14** **15**

**15**). Ketone **13** was prepared by a straightforward four-step route from (*R*)-fructose.[6] Aldehydes **14** and **15** were prepared by literature procedures.[7-9] Ketone **13** was converted into its lithium enolate by reaction with lithium diisopropylamide in THF at −78 °C. One equivalent of either **14** or **15** was added at the same temperature and the reaction mixture was quenched after a reaction time of 20 min. Stereoisomeric mixtures were obtained in each case and were analyzed by $^{13}$C NMR and by high pressure liquid chromatography. In several runs with both aldehydes, the condensation yield was uniformly good (85–94%). Reaction of **13** with **14** affords a mixture of

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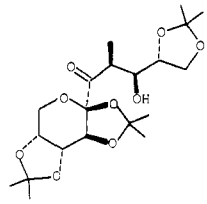
three aldols in a ratio of 5.5:2.5:1. The two major products were isolated by chromatography and shown to have the stereostructures **16** (61%) and **17** (28%) by a combination of $^{13}C$



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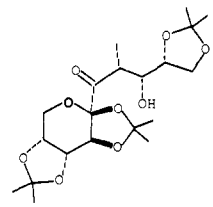

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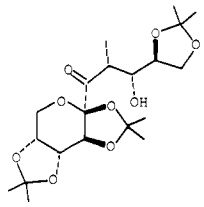

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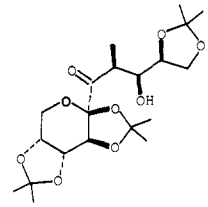

19

NMR[10] and circular dichroism.[11] The minor isomer from this condensation must be a threo diastereomer from its $^{13}C$ NMR spectrum.[10]

In contrast, the similar reaction of **13** with aldehyde **15** affords only two stereoisomers, in a ratio of 13:1. The major isomer was shown to have structure **18** by its $^{13}C$ NMR and CD spectra;[10,11] the minor isomer has the threo configuration. None of the alternate erythro isomer **19** could be detected under conditions where we could detect as little as 3% of a minor diastereomer.

Thus, the principle of double stereodifferentiation is vividly demonstrated; in this case the 1,2 diastereoselectivity exhibited by the aldehyde is increased from 2:1 to >30:1. We have observed similar results with another chiral ethyl ketone. Further application of the strategy in synthesis is reported in the following communication.

**Acknowledgment.** Support for this research was provided by a grant from the U.S. Public Health Service (NIH Grant AI-15027).

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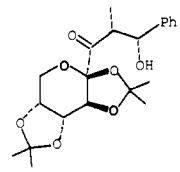
(9) We thank Mr. Steven Young for preparing aldehydes **14** and **15**.
(10) See ref 1. In brief, structure assignments may be made based on the $^{13}C$ NMR chemical shift of the methyl carbon resonance adjacent to the carbonyl group. In erythro diastereomers this resonance occurs in the range 8–13 ppm, while in threo diastereomers it is in the range 13–18 ppm.
(11) The CD method that we have employed to make these assignments may be summarized as follows. Condensation of ketone **13** with benzaldehyde affords two erythro diastereomers in a ratio of 3.7:1. The major isomer (mp 82–84 °C) was shown by single-crystal X-ray analysis to have structure **20**. Thus, the minor isomer (mp 105–107 °C) is the other erythro diastereomer **21**. The CD spectra of **13**, **20**, and **21** are as follows: **13**, $[\theta]_{295}$ +1500; **20**, $[\theta]_{300}$ +8900; **21**, $[\theta]_{313}$ −2500. Thus, the $\alpha R,\beta R$ configuration in the aldol results in a slight red shift in the absorption, accompanied by a large increase in $[\theta]$. On the other hand, the $\alpha S,\beta S$ configuration at these two centers results in a more pronounced red shift and a more negative $[\theta]$. The CD spectra of aldols **16**, **17**, and **18** follow: **16**, $[\theta]_{325}$ +460; **17**, $[\theta]_{297}$ +4000; **18**, $[\theta]_{300}$ +3250.



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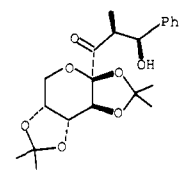

21

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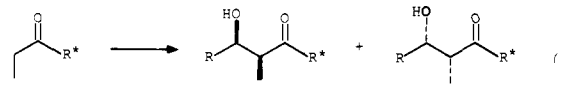
## Acyclic Stereoselection. 6. A Reagent for Achieving High 1,2 Diastereoselection in the Aldol Conversion of Chiral Aldehydes into 3-Hydroxy-2-methylcarboxylic Acids

*Sir:*

In the accompanying communication[1] we demonstrate the utility of double stereodifferentiation for enhancing the 1,2 diastereoselectivity ("Cram's rule selectivity") of chiral aldehydes. In order for this strategy to be employed for the synthesis of $\beta$-hydroxy acids and aldehydes, we need a readily available ethyl ketone (**1**) which possesses several properties. First, the group R* must be large, so that the resulting enolate will show high erythro selectivity.[2] Second, R* must be easily convertible into OH or H. Finally, R* must be chiral and the resulting enolate must show substantial stereoselectivity (1,3 diastereoselectivity) in its reactions with achiral aldehydes, since the greater the ratio of **2** to **3** (eq 1), the more effective



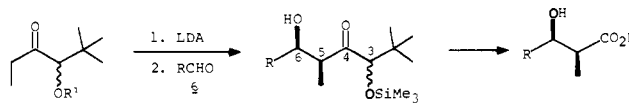
(1)

1 2 3

**1** will be in enhancing 1,2 diastereoselectivity in its reactions with chiral aldehydes. In this communication, we report the synthesis and some reactions of such a reagent.

Ketone **5** has been prepared by two routes. In one method, 1-lithio-1-methoxypropene[3,4] is added to pivaldehyde (pentane, −60 °C). After hydrolysis of the enol ether (0.1 N methanolic HCl, 30 min, 25 °C), hydroxy ketone **4** is produced in 54% yield. Alternatively, 5-methylhex-4-en-3-one[5] is allowed to react with lithium dimethylcopper (ether, 0 °C) and the resulting enolate mixture quenched with trimethylsilyl chloride and triethylamine to obtain a silyl enol ether. The crude ether is oxidized using *m*-chloroperoxybenzoic acid ($CH_2Cl_2$, 0 °C, 1 h),[6] and the oxidation product is hydrolyzed (1.2 N aqueous HCl–ether, 25 °C, 3 h) to obtain hydroxy ketone **4** in 56% yield. **4** is heated at 100 °C for 24 h with bis(trimethylsilyl)-acetamide[7] to obtain **5** (40% overall yield).

Ketone **5** is converted into its enolate by reaction with lithium diisopropylamide in THF (0.25 M, −70 °C, 2 h). Te-




4: R' = H
5: R' = $SiMe_3$

a: R = $Ph_2CH$
b: R = $PhCH_2$
c: R = $(CH_3)_2CH$
d: R = $(CH_3)_3C$
e: R = Ph

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