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# Concerning the Application of the $^1$H NMR ABX Analysis for Assignment of Stereochemistry to Aldols Deriving from Aldehydes Lacking $\beta$-Branches

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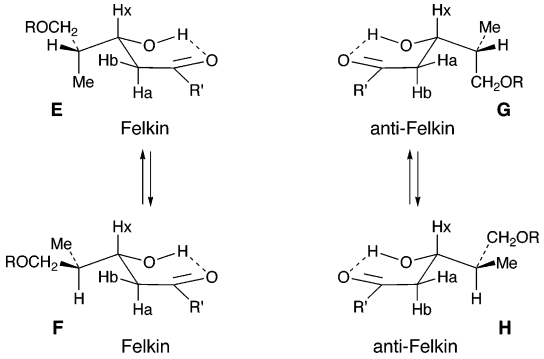


Attempts to apply the $^1$H NMR ABX method for assignment of stereochemistry of $\beta$-hydroxy ketones to aldols **4**−**10** deriving from α-methyl aldehydes lacking $\beta$-branches reveals that the presence of a $\beta$-branch in the aldehyde reaction partner is necessary so that the average chemical environment of Ha and Hb is different for the Felkin and anti-Felkin aldols (see conformational pairs **A/B** and **C/D**, respectively). When the chiral α-methyl aldehyde lacks a $\beta$-branch, as in the case of the aldehyde precursors to **4**−**10**, the conformational energies of **E** and **F** (for the Felkin $\beta$-hydroxy ketone derivatives), and conformers **G** and **H** for the anti-Felkin aldols, are too close in energy (within each pair), such that the average chemical and magnetic environments of Ha and Hb in the two diastereomers cannot be easily distinguished. This analysis provides a rational basis for application of the $^1$H NMR ABX pattern analysis to other $\beta$-hydroxy ketone derivatives.

## Introduction

During studies on aldol addition reactions of enolborinates from α-methyl-$\beta$-alkoxy methyl ketones,[1] we (the Campinas group) have examined boron-mediated aldol reactions of methyl ketones **1**−**3** with chiral aldehydes leading to aldol adducts **4**−**11** (Figure 1).[2−6] These compounds appeared ideally suited for stereochemical analysis by using the very simple method for assigning the relative stereochemistry of $\beta$-hydroxy ketones reported in 2002 by Roush and co-workers.[7]

This method involves analysis of the ABX system for the methylene unit α to the carbonyl group in the $^1$H NMR spectra of the $\beta$-hydroxy ketones.[2,7] The Michigan group reported that the $^1$H NMR spectra (measured in $CDCl_3$ or $C_6D_6$) of aldol adducts with 3,4-syn (or Felkin) stereochemistry exhibit a characteristic doublet of dou-

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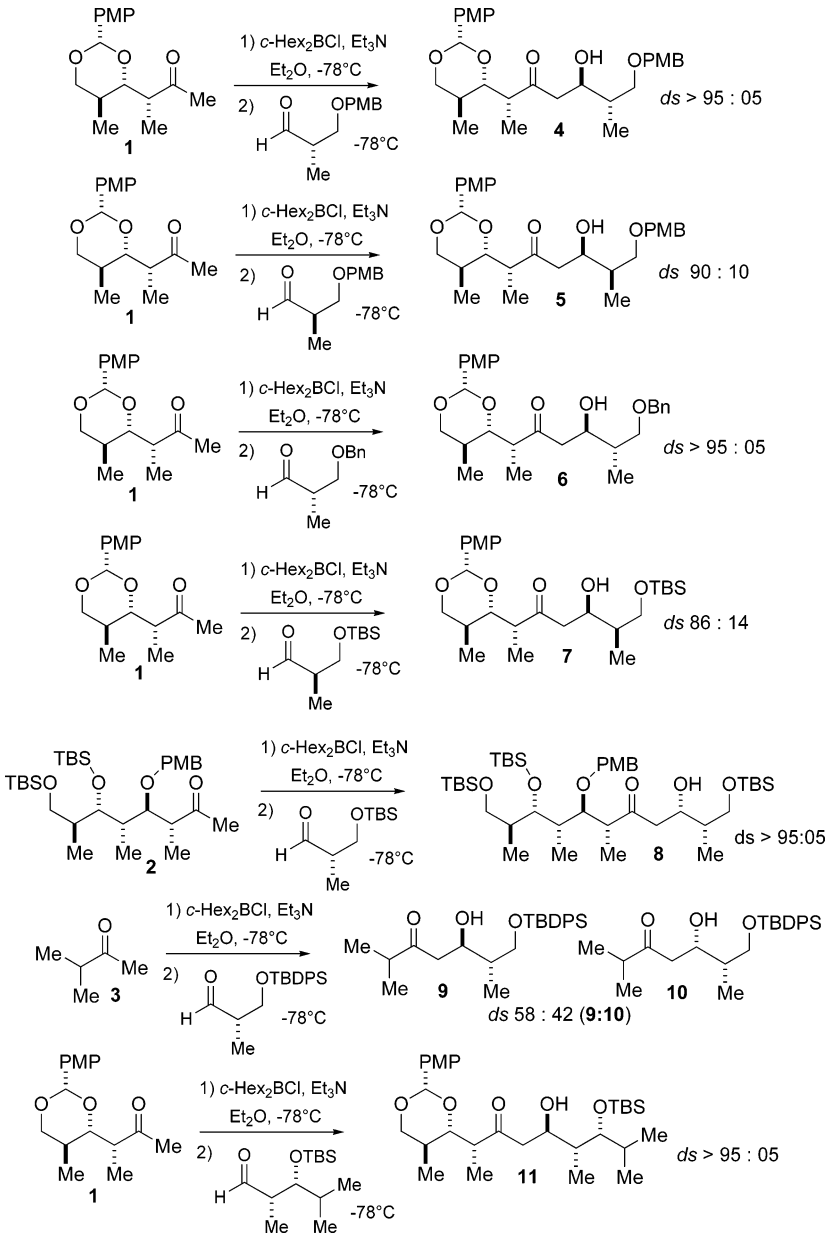


**FIGURE 1.** Synthesis of aldols **4**−**11**.

blet for Ha with a large $J_{a,x}$ (7.8−10.0 Hz) downfield of the resonance for Hb, which shows a small $J_{b,x}$ (1.1−5.4 Hz). For anti-Felkin aldol adducts (3,4-anti), the $^1$H NMR displays the downfield resonance for Ha with a small $J_{a,x}$ (1.5−2.8 Hz), and the higher field resonance for Hb, with a larger $J_{b,x}$ (9.2−12.5 Hz). These results are consistent with the aldols adopting the internally hydrogen-bound conformations indicated in Figure 2.

It was also noted that Hb of the anti-Felkin diastereoisomers appears downfield from Hb of the Felkin isomer, while Ha of the Felkin aldol appears downfield of Ha in the anti-Felkin diastereoisomer. The authors also observed that Hx resonance for the Felkin aldols appears downfield of Hx in the corresponding anti-Felkin diastereomers.[7]

Reported herein is a refinement of the previously reported model,[7] supported by data for aldols **4**−**11**, that demonstrates that a $\beta$-branch in the original aldehyde reaction partner is necessary to create magnetically distinct NMR environments for Ha and Hb in the diastereomeric aldol products.

## Results and Discussion

Pertinent $^1$H NMR data for compounds **4**−**11** appear in Figure 3 and Table 1. During attempts to assign the relative stereochemistry of aldols **4**−**11** by using the

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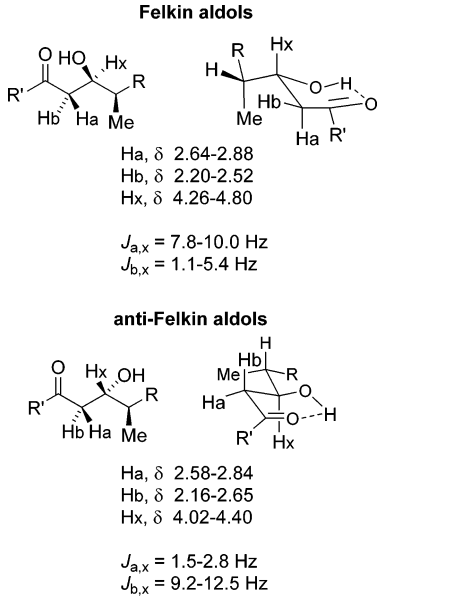



**FIGURE 2.** Summary of the $^1$H NMR ABX pattern analysis for stereochemical assignments of $\beta$-hydroxy ketones.

**TABLE 1. Selected $^1$H NMR Data for Aldols 4−11**[a]

| compd | Ha ($\delta$) | Hb ($\delta$) | $J_{a,x}$ (Hz) | $J_{b,x}$ (Hz) |
|---|---|---|---|---|
| **4** | 2.73 | 2.58 | 8.7 | 3.0 |
| **5** | 2.73 | 2.51 | 9.0 | 3.3 |
| **6** | 2.72 | 2.58 | 8.9 | 3.0 |
| **7** | 2.76 | 2.49 | 9.5 | 2.9 |
| **8** | 2.71 | 2.55 | 8.7 | 2.9 |
| **9**[b] | 2.40 | 2.29 | 8.9 | 2.9 |
| **10**[b] | 2.41 | 2.18 | 9.3 | 2.7 |
| **11** | 2.78 | 2.58 | 2.6 | 8.6 |

[a] All NMR data are reported in $C_6D_6$ as solvent except for aldol **11** (measured in $CDCl_3$). [b] $^1$H NMR data for **9** and **10** were measured in the 58:42 diastereoisomeric mixture.

NMR method reported by Roush and co-workers,[7] we observed that in all of the cases studied with aldehydes lacking $\beta$-branching, leading to aldols **4**−**10**, the downfield resonance for Ha exhibits a doublet of doublet with a large coupling constant. On the basis of the results disclosed by Roush et al.,[7] this should be consistent with a Felkin aldol product.

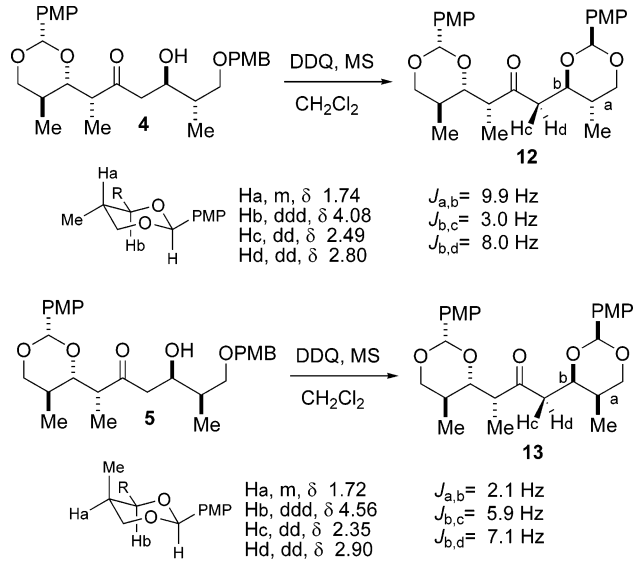
However, in one of the cases—specifically aldol **4**—we prepared the corresponding benzylidene acetal **12** by treatment of **4** with DDQ (Scheme 1).[8] Analysis of the $^1$H NMR coupling constants, specifically $J$ = 9.9 Hz, proved that Ha and Hb are both axial in **12**. This indicates that benzylidene acetal **12** derives from an anti-Felkin aldol product.

Similarly, the relative stereochemistry of aldol **5** was determined after conversion to the *p*-methoxybenzylidene acetal **13** by DDQ oxidation of the PMB ether. The coupling constant measured between Ha and Hb ($J$ = 2.1 Hz) in **13** confirmed the Felkin stereochemistry for aldol **5**.

In contrast to the situation with **4**−**10**, the $^1$H NMR data measured for compound **11** were completely consistent with the assignment of the anti-Felkin aldol stereochemistry by application of the ABX NMR method.[7]

(8) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.

**SCHEME 1. Stereostructure Assignments for Aldols 4 and 5**




The vast majority of the compounds examined in the 2002 Roush paper[7] were aldols deriving from $\beta$-branched aldehydes with a large "R" group (as is the case for the aldol reaction leading to **11**).[9] In these cases, conformation **A** (Figure 4) is believed to be the major conformer for the Felkin diastereomers, as the large "R" substituent is positioned anti to C$\alpha$−C$\beta$ in the internally hydrogen-bound conformation of the aldol product.[7,10] (In contrast, the "R" substituent is in a higher energy gauche relationship with C$\alpha$−C$\beta$ in **B**.) Similarly, conformation **D** is believed to be the most important for the anti-Felkin aldols, when the "R" substituent is branched (note the gauche relationship between "R" and C$\alpha$−C$\beta$ in conformation **C**). As long as these conformational preferences apply, Ha and Hb in the Felkin and anti-Felkin aldol products are in very different (average) magnetic environments, giving rise to the characteristic visual and diagnostic ABX $^1$H NMR patterns previously described.[7]

The situation is much different for aldols deriving from aldehydes lacking $\beta$-branches (such as **4**−**10**, vide supra). In these cases, the steric size of "ROCH$_2$−" and "Me−" is comparable, and as a result the difference in energy between conformations **E** and **F** for the Felkin aldol diastereomers, and between **G** and **H** for the anti-Felkin diasteomers, is negligible (Figure 5). Conformers **E** and **G** are pseudo-enantiomeric, as are **F** and **H**. Consequently, the average chemical environment of Ha and Hb in the two diastereomers is comparable, and the NMR properties of $H_a$ (and $H_b$) in the Felkin and anti-Felkin diastereomers are not easily distinguishable.

In conclusion, the data summarized here for aldols **4**−**10** demonstrate that the $^1$H NMR ABX method for assignment of stereochemistry of $\beta$-hydroxy ketones is of limited utility for aldols deriving from α-methyl

(9) Only one set of aldols deriving from an aldehyde lacking a $\beta$-branch was presented in the 2002 *J. Org. Chem.* paper—compounds **27** and **49** reported therein (ref 7). The data for **27** were consistent with the $^1$H ABX NMR pattern analysis, but the coupling constants and proton assignments for anti-Felkin aldol **49** could not be made (as reported in footnote *e* of Table 2 in the 2002 publication).

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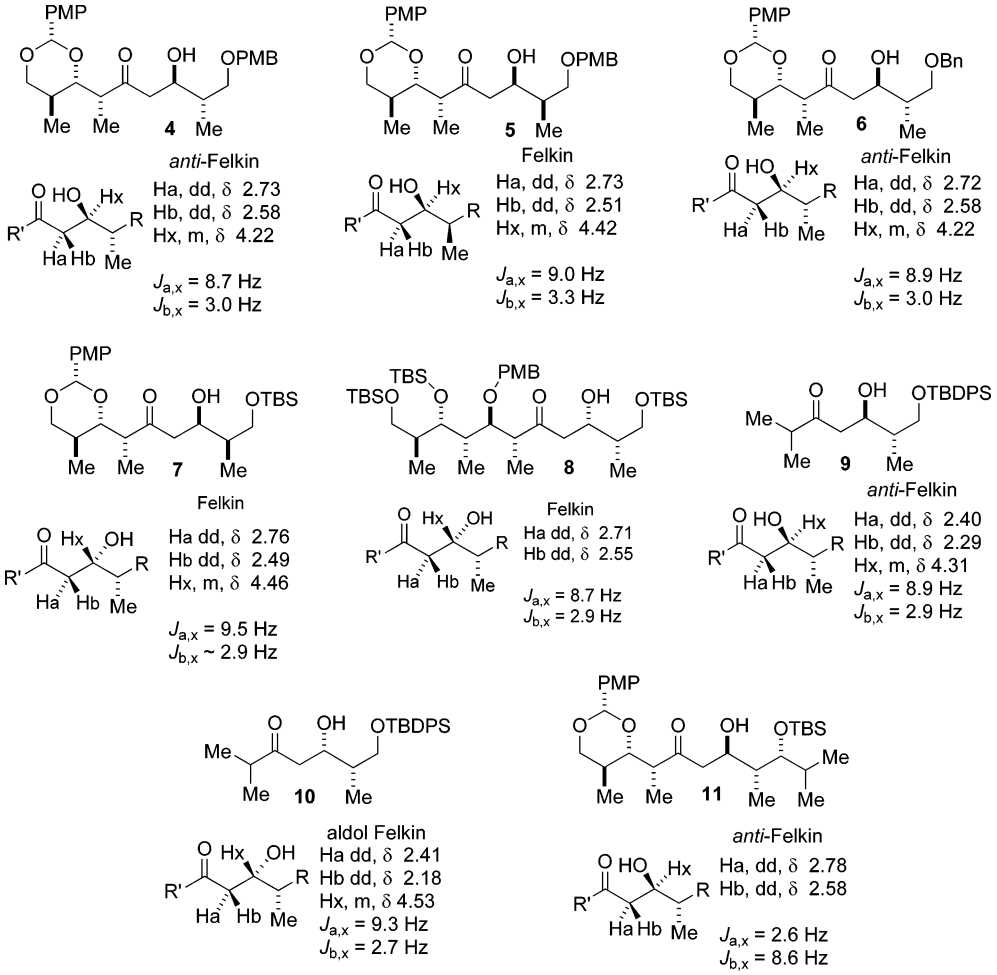


**FIGURE 3.** $^1$H NMR characterization of aldols **4**−**11**.

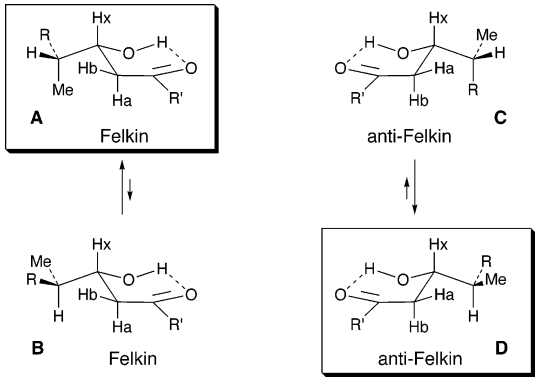


**FIGURE 4.** Hydrogen-bound conformations of Felkin and anti-Felkin $\beta$-hydroxy ketones in Cases where "R" is a large (branched) substituent.

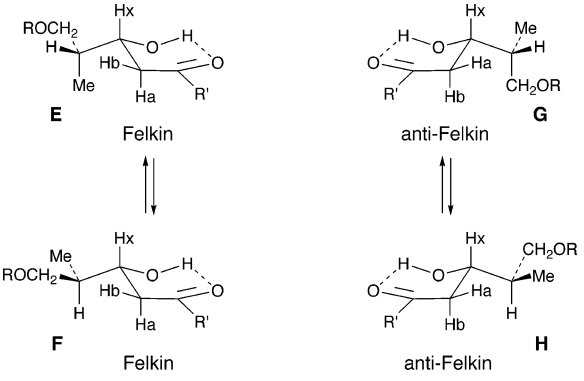


**FIGURE 5.** Analysis of the hydrogen-bound conformations of Felkin and anti-Felkin $\beta$-hydroxy ketones in cases where the $\beta$-carbon of the precursor RCHO is unbranched.

aldehydes lacking $\beta$-branches. The presence of the $\beta$-branch in the aldehyde reaction partner is necessary so that the average chemical environment of Ha and Hb is different for the Felkin and anti-Felkin aldols (see conformational pairs **A/B** and **C/D**, respectively). When the chiral α-methyl aldehyde lacks a $\beta$-branch, as in the case of the aldehyde precursors to **4**−**10**, the conformational energies of **E** and **F** (for the Felkin $\beta$-hydroxy ketone derivatives), and conformers **G** and **H** for the anti-Felkin aldols, are too close in energy (within each pair), such that the average chemical and magnetic environments of Ha and Hb in the two diastereomers cannot be easily distinguished. In such cases, one must resort to chemical derivatization methods to make appropriate stereochemical assignments.

The analysis presented herein provides a rational basis for other investigators to apply the $^1$H NMR ABX pattern analysis to other $\beta$-hydroxy ketone derivatives.

## Experimental Section[11]

**Representative Procedure for Methyl Ketone Aldol Reaction.** Dicyclohexylboron chloride (1.5 equiv) was added to a cooled (0 °C) solution of the corresponding methyl ketone (1.5 equiv) in $CH_2Cl_2$ (8 mL), followed by dropwise addition of $Et_3N$ (1.7 equiv), leading to the precipitation of $Et_3N{\cdot}HCl$. The resulting white heterogeneous reaction mixture was stirred at 0 °C for 1 h, then cooled to −78 °C, and a solution of the aldehyde (1.5 equiv) in $CH_2Cl_2$ was added dropwise (aldehyde was added as a 1.0 M solution in $CH_2Cl_2$). After 4 h at −78 °C and 10 h at −20 °C, the reaction mixture was quenched by addition of 7 mL of a pH 7 buffer/MeOH solution (1/6, v/v), and 2 mL of a 30% $H_2O_2$/MeOH (1/2, v/v) solution. The ice bath was removed and the reaction was allowed to warm to room temperature and stirred for 1 h. The solution was diluted with $CH_2Cl_2$ and water, the layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the products by silica gel chromatography gave the aldol adducts.

(11) New compounds and the isolated intermediates gave satisfactory $^1H$ and $^{13}C$ NMR, IR, and HRMS data. Yields refer to chromatographically and spectroscopically homogeneous materials. Tabulations of spectroscopic data are provided in the Supporting Information.

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**Supporting Information Available:** Product characterization for compounds **4**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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