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# A Convenient Method for the Assignment of Relative Configuration of Acyclic α-Alkyl-β-hydroxy Carbonyl Compounds by $^1$H NMR

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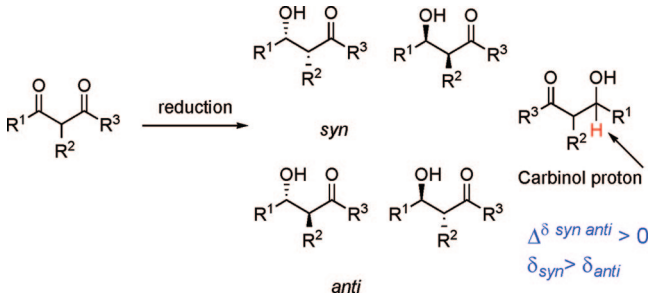


The relative configuration of acyclic α-alkyl-β-hydroxy carbonyl compounds can be determined by using $^1$H NMR spectroscopy. The assignment can be achieved by recording the $^1$H NMR spectrum of the *syn*−*anti* mixture. The upfield carbinol hydrogen signal belongs to the *anti* whereas the downfield to the *syn* stereoisomer.

Recently, various methods for the assignment of the absolute configuration of chiral compounds based on NMR spectroscopy have emerged. The two general approaches involve (a) the derivatization of the substrate with unknown configuration with both enantiomers of a chiral derivatizing agent (CDA) followed by NMR analysis of the thus produced diastereomeric derivatives and (b) the NMR analysis of the sample in a chiral environment.[1] The determination of the relative configuration is very important for the assignment of the absolute configuration of chiral organic compounds bearing more than one stereogenic center. In particular, the assignment of the relative configuration of secondary alcohols,[2] diols,[3] triols,[4] and polyols[5] by NMR analysis has been reported.

α-Alkyl-β-hydroxy carbonyl compounds are very important in asymmetric organic synthesis. They have been used as chiral building blocks in the synthesis of polyketides, statins, protease inhibitors, and other important pharmaceuticals.[6] Elucidation of their relative configuration is of particular interest due to their presence in many classes of natural products. The only method for acyclic molecules developed by the use of $^{13}$C NMR analysis is the well-established Heathcock observation,[2] which has been used for α-methyl-β-hydroxy carbonyl compounds.

We have recently been interested in the enzymatic reduction of α-alkyl-1,3-diketones and α-alkyl-β-keto esters for the stereoselective synthesis of chiral α-alkyl-β-hydroxy ketones or esters utilizing isolated, NAD(P)H-dependent ketoreductases.[7,8] Two among these molecules are the natural pheromones Sitophilure[9] and Sitophilate.[10] A number of α-mono- or dialkyl-substituted-β-hydroxy ketones and esters were prepared in optically pure form, as single diastereomers from the same starting substrate depending on the choice of enzymes. In that work,[8] their absolute configurations have been determined by conventional methods, using (+)- or (−)-methoxyphenylacetic acid (MPA) as a chiral derivatizing agent. The chemical shift's trend observed in the carbinol hydrogen signal led us to propose a new empirical and easy to use method for assigning the relative configuration of these compounds.

We now report a simple method for the elucidation of relative configuration based on our observations in the $^1$H NMR spectra of a series of ten different α-alkyl-β-hydroxy ketones, eight different α-alkyl-β-hydroxy esters, as well as one α-alkyl-β-hydroxy carboxylic acid. Certain $^1$H NMR chemical shifts of all the above compounds presented here demonstrate how the new empirical method can be used for assigning the relative configuration of this class of compounds.

The chemical reduction of α-alkyl-1,3-dicarbonyl compound leads to the formation of two possible diastereomeric compounds, the *syn* and the *anti* diastereomer (Figure 1). One characteristic signal in the $^1$H NMR spectra of these compounds is that of the carbinol proton. The observation of the chemical shifts of this proton allows the assignment of the relative configuration of α-alkyl-β-hydroxy carbonyl compounds.

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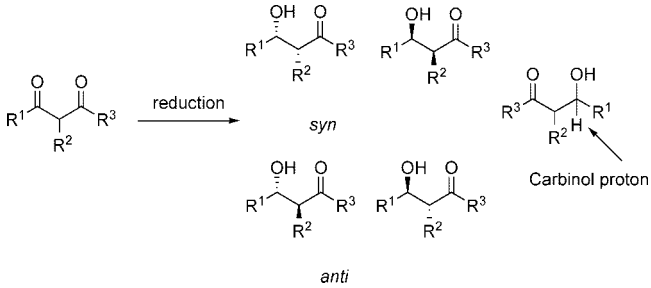


**FIGURE 1.** *Syn* and *anti* diastereomers from the reduction of α-alkyl-1,3-dicarbonyl compounds.

**TABLE 1. $^1$H NMR Chemical Shifts of Carbinol Proton in Compounds 1−19**

| Entry | Hydroxy Compound | Carbinol proton[a] | | $\Delta^{\delta\ syn\ anti}$ (ppm)[a] |
|---|---|---|---|---|
| | | *syn* (ppm) | *anti* (ppm) | |
| 1 | **1** | 4.126 | 3.914 | 0.212 |
| 2 | **2** | 3.997 | 3.948 | 0.049 |
| 3 | **3** | 3.979 | 3.912 | 0.067 |
| 4 | **4** | 3.968 | 3.859 | 0.109 |
| 5 | **5** | 4.025 | 3.936 | 0.089 |
| 6 | **6** | 3.982 | 3.910 | 0.072 |
| 7 | **7** | 4.020 | 3.929 | 0.091 |
| 8 | **8** | 3.806 | 3.609 | 0.197 |
| 9 | **9** | 4.089 | 3.904 | 0.185 |
| 10 | **10** | 4.246 | 4.108 | 0.138 |
| 11 | **11** | 4.062 | 3.872 | 0.190 |
| 12 | **12** | 3.979 | 3.925 | 0.054 |
| 13 | **13** | 4.014 | 3.928 | 0.086 |
| 14 | **14** | 3.991 | 3.909 | 0.082 |
| 15 | **15** | 3.809 | 3.587 | 0.222 |
| 16 | **16** | 3.805 | 3.583 | 0.222 |
| 17 | **17** | 3.800 | 3.568 | 0.232 |
| 18 | **18** | 3.876 | 3.640 | 0.236 |
| 19 | **19** | 3.935 | 3.869 | 0.066 |

[a] All chemical shifts and the $\Delta^{\delta syn\ anti}$ were measured from the $^1$H NMR spectra of the corresponding chemically formed *syn*−*anti* mixtures in $CDCl_3$ solution.

After the synthesis of 19 α-alkyl-β-hydroxy carbonyl compounds chemically and in optically pure form, we observed that in every case the *anti* carbinol proton signal exhibits persistent upfield shift from the corresponding *syn* proton. These results are summarized in Table 1. The chemical shift of the carbinol hydrogen of a series of hydroxy carbonyl compounds **1**−**19** shows a substantial downfield resonance for the *syn* compared to the *anti* stereoisomer. This persistent positive difference between chemical shifts $\Delta^{\delta\ syn\ anti}$ of the carbinol hydrogens ranges between 0.049 (entry 2) and 0.236 ppm (entry 18) (Table 2). In all cases a positive $\Delta^{\delta\ syn\ anti}$ ($\delta_{syn} > \delta_{anti}$) difference in the chemical shifts of the *syn/anti* carbinol protons in the chemically formed *syn*−*anti* mixture is systematically observed. This substantial and positive chemical shift difference can distinguish between *syn* and *anti* products. In all the studied compounds, the carbinol proton signal of the *syn* diastereomer appears between 3.800 (entry 17) and 4.246 ppm (entry 10), while that of the *anti* diastereomer appears between 3.568 (entry 17) and 4.108 ppm (entry 10).

**TABLE 2. Chemical Shift Range for Carbinol Proton**

| relative configuration | carbinol proton (ppm) | $\Delta^{\delta\ syn\ anti}$ (ppm) |
|---|---|---|
| *syn* | 3.800−4.246 | 0.049−0.236 |
| *anti* | 3.568−4.108 | |

Two representative spectra from compounds **7** and **17**, entries 7 and 17, respectively, are shown in Figure 2. For example, hydroxy ester **17** (entry 17) impressively illustrates this point. In the chemically formed *syn*−*anti* mixture, the $H_{syn}$ and $H_{anti}$ show a large and positive chemical shift difference of $\Delta^{\delta\ syn\ anti} = 0.232$ ppm, whereas in the pure stereoisomers *syn* and *anti*, only the corresponding $H_{syn}$ and $H_{anti}$ signals are shown. Similarly, hydroxy ketone **7** shows again downfield $H_{syn}$ accompanied by an upfield $H_{anti}$ resonance, with a positive difference of $\Delta^{\delta\ syn\ anti} = 0.091$ ppm.

Therefore, by a simple observation of the carbinol hydrogen chemical shift of the chemically formed *syn*−*anti* mixture the relative configuration of the optically pure diastereomers is easily assigned.

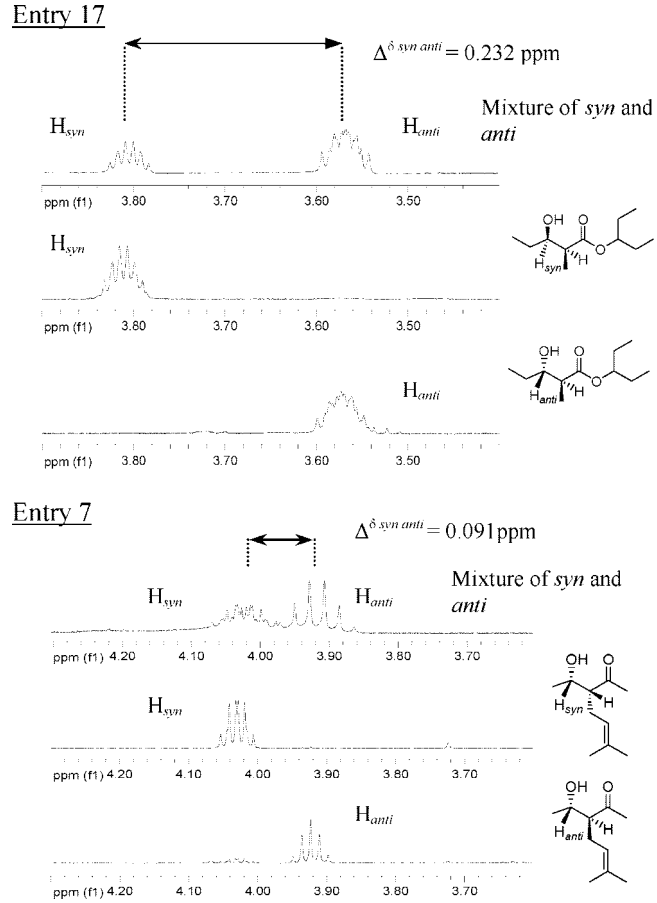


**FIGURE 2.** Assignment of the $\Delta^{\delta\ syn\ anti}$ of carbinol protons by $^1$H NMR.

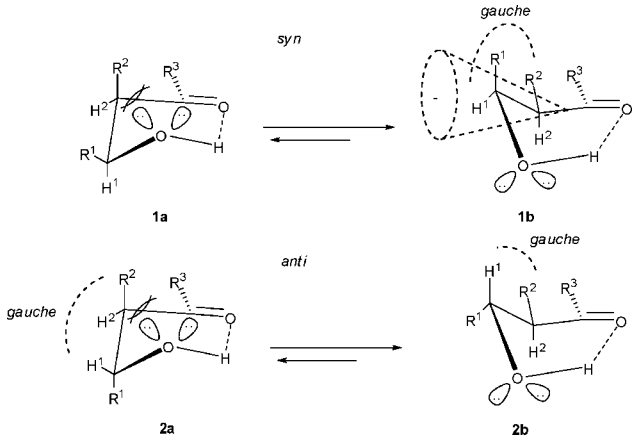


**FIGURE 3.** Half-chair-like conformers of α-alkyl-β-hydroxy carbonyl compounds.

In these acyclic molecules (α-alkyl-β-hydroxy carbonyl compounds), an intramolecular hydrogen bond between the 1,3 hydroxy and the keto groups is proposed. This hydrogen bond is responsible for a half-chair conformation of the two diastereomers (Figure 3).[11]

The upfield shift of carbinol proton ($H^1$) of the *anti* diastereomer can be explained by the effect of magnetic anisotropy and/or by the *gauche* interactions of carbinol hydrogen $H_1$.

In previous studies, the upfield shift of axial protons relative to equatorial in cyclohexane conformations[12] was rationalized in terms of the magnetic anisotropy.[13] This effect may rationalize the order of the chemical shifts between the *anti* and *syn* carbinol protons in the β-hydroxy carbonyl compounds **1**−**19**. Comparing the conformers of *syn* and *anti* diastereomers in Figure 3, the conformers **1b** and **2b** must be more stable than **1a** and **2a**, respectively, due to the small 1,3-interactions between the $R^2$ group and the nonbonding electrons of hydroxy oxygen. Between the more stable conformations **1b** and **2b** only the **1b** has the hydrogen $H^1$ in the equatorial position. Because of the magnetic anisotropy effect, the equatorial carbinol proton is deprotected compared to the axial $H^1$ in conformer **2b**. Therefore, the *anti* carbinol proton $H^1$ (**2b**) is upfield shifted.

The upfield shift of the carbinol proton ($H^1$) of the *anti* diastereomer can also be explained by examining the *gauche* interactions of this proton in all conformers (Figure 3). The *syn* stereoisomer has one *gauche* interaction between the hydrogen $H^1$ and group $R^2$ in the **1b** conformer, whereas in the *anti* stereoisomer these *gauche* interactions appear in both conformers **2a** and **2b**. Therefore, the upfield shift can be attributed to the more sterically hindered $H_{1anti}$ (two $H^1 \leftrightarrow R^2$ *gauche* interactions) in **2a** and **2b**, compared with the less hindered $H_{1syn}$ (only one $H^1 \leftrightarrow R^2$ *gauche* interaction) in **1b**.

In conclusion, the relative configuration of acyclic α-alkyl-β-hydroxy carbonyl compounds has been determined by using $^1$H NMR spectroscopy. The assignment can be achieved by recording the $^1$H NMR spectrum of the chemically formed *syn*−*anti* mixture (which can be obtained easily by a chemical reduction) followed by a simple chemical shift comparison with the corresponding spectrum of the optically pure hydroxy compound. The relative configuration also can be assigned easily in any mixture of the hydroxy carbonyl diastereomers. In this case a simple $^1$H NMR spectrum reveals the relative configuration. The downfield carbinol hydrogen signal belongs to the *syn* whereas the upfield to the *anti* stereoisomer. This straightforward method does not require any chemical modification or derivatization before the assignment of the relative configuration.

## Experimental Section

$^1$H NMR spectra were recorded on a 300 or a 500 MHz spectrometers in $CDCl_3$ solutions, by using $Me_4Si$ as internal standard. Chemical shifts are reported in ppm downfield from $Me_4Si$. Compounds **1**−**19** were prepared chemically as a *syn-anti* mixture according to the literature.[7,8] *Syn* or *anti* hydroxy ketones **1**−**10**, and hydroxy esters **11**−**19** in pure form were prepared by enzymatic reduction of the corresponding 1,3-diketones or keto esters accordingly, by using NADPH-dependent ketoreductases, as we have recently reported.[7,8,10]

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**Supporting Information Available:** General analytical method and $^1$H NMR spectral data for compounds **1**−**19** in racemic, *anti* and *syn* configuration and copies of the complete $^1$H NMR spectra of chemically formed *syn*−*anti* mixture, *anti* and *syn* configuration for compounds **1**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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