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Improved Method for the Assignment of the Relative Configuration of 1,3-Diols, by Using ^{13}C-Enriched Acetonides

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Abstract: A facile preparation of ^{13}C-enriched acetonides for the determination of the relative stereochemistry of 1,3-diols is described. The method allows *inter alia* the detection of minor diastereomers arising from the synthesis of 1,3-diols.

The inspection of the ^{13}C chemical shift of the acetonide methyl groups of 1,3-diols is a valuable tool currently used for the determination of the relative stereochemistry of 1,3-diols. The bases of the method were outlined by Buchanan *et al.*[1] and then widely expanded by Richnovsky *et al.*[2,3]. In short, since a *syn*-acetonide exists in a well defined chair conformation, the acetonide methyls resonate at two distinct chemical shift values at *ca.* 20 and 30 δ; an *anti*-acetonide exists in a twist-boat conformation and the acetonide methyls resonate very close in the δ 25 zone. However, minor drawbacks of the technique are dependent i) on the relative lack of sensitivity of ^{13}C NMR spectroscopy when a small amount of a complex substance is available (typically with natural products); and ii) on the presence of a large number of methyl groups such as in polypropionate derived compounds which could make problematic the assignment of the chemical shift of the acetonide methyl groups. In this latter case it has been suggested[4] that the chemical shift of the acetal carbon could be used for the determination of the relative stereochemistry of the diol, although anomalies have been noted[3].

It has been suggested[3] that the sensitivity of the method could be increased 100-fold by preparation of ^{13}C-enriched acetonides. However, in our knoweledge the use of ^{13}C-enriched acetonides has been exploited only in the determination of the stereochemistry of the macrolactins[5]. In this case the ^{13}C-enriched acetonides were prepared following the Noyori's procedure[6] which implies at first silylation of the diol and then reaction with [1,3-$^{13}C_2$]acetone in the presence of TMSOTf and in strictly aprotic conditions. In our hands, as also previously experienced[5], this method gave very poor yields when small amounts of material were available (1-3 mg) and we wish to report that ^{13}C-enriched acetonides could be more practically prepared by using 1,3-^{13}C-enriched 2,2-dimethoxypropane. This latter was prepared *in situ* by reacting 2,2-dimethoxypropane with commercially available [1,3-$^{13}C_2$]acetone.

The assignment of the ^{13}C chemical shift of the methyls in acetonides enriched in such a way, and hence of the relative stereochemistry, is straightforward because i) the enriched signals dominate the spectrum and ii) each methyl signal appears as a doublet because of the $^2J_{CC}$ between the two acetonide methyls. The J value was *ca.* 4.5 Hz in *syn*-acetonides and *ca.* 6.5 Hz in *anti*-acetonides and they arise by examination of several model compounds, natural[7], synthetic[8] and commercially available. The geminal coupling, which was not noted

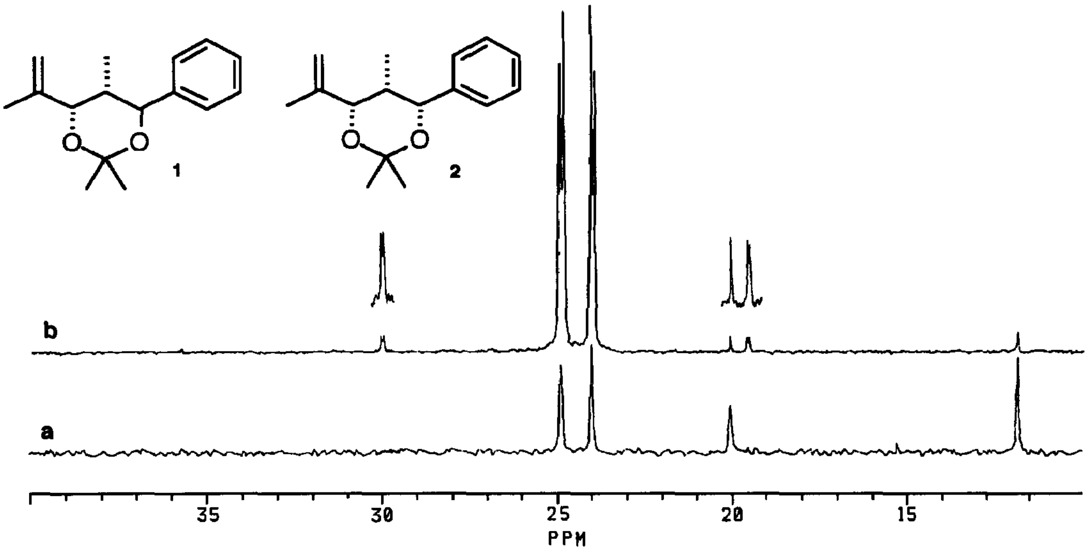

Fig. 1. Methyl resonance zone of the ^{13}C-NMR spectra of the mixture of the acetonides **1** (major) and **2**. a) Natural abundance and b) ^{13}C-enriched. The spectra were recorded with a Bruker AM 250 at 62.89 MHz.

earlier[5], is very useful since it allows, for example, the detection of small amounts of minor diastereomers during the synthesis of 1,3-diols. In Fig. 1 the ^{13}C-NMR spectra of the acetonides (both natural abundance and ^{13}C-enriched) of the mixture of compounds **1** and **2** are reported. In the natural abundance spectrum the presence of the *syn*-diastereomer was not detected, while in the ^{13}C-enriched acetonide it is clearly visible. Integration of the inverse gated ^{13}C-NMR spectrum of the ^{13}C-enriched sample showed that the *syn*-acetonide **2** represent the 3.2% of the mixture.

Preparations of ^{13}C-enriched acetonides. A stock solution was prepared by dissolving [1,3-$^{13}C_2$]acetone (250 mg; 98 atom % ^{13}C; Aldrich) in dry toluene (1 ml). To 0.25 ml of the stock solution, 0.25 ml of 2,2-dimethoxypropane were added together with a crystal of p-TsOH and the solution was left to stand at r.t. for 7 h. The above solution was added to 1-30 mg of diol and the mixture was left to stand overnight at r.t. and then filtered through a short Al_2O_3 column. In order to enhance resolution for the observation of the $^2J_{CC}$ coupling, the ^{13}C-NMR spectra were obtained from 32K free induction decay signals.

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