

Application of the modified Mosher's method to linear 1,3-diols

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Received 9 January 1999; revised 15 February 1999; accepted 19 February 1999

Abstract

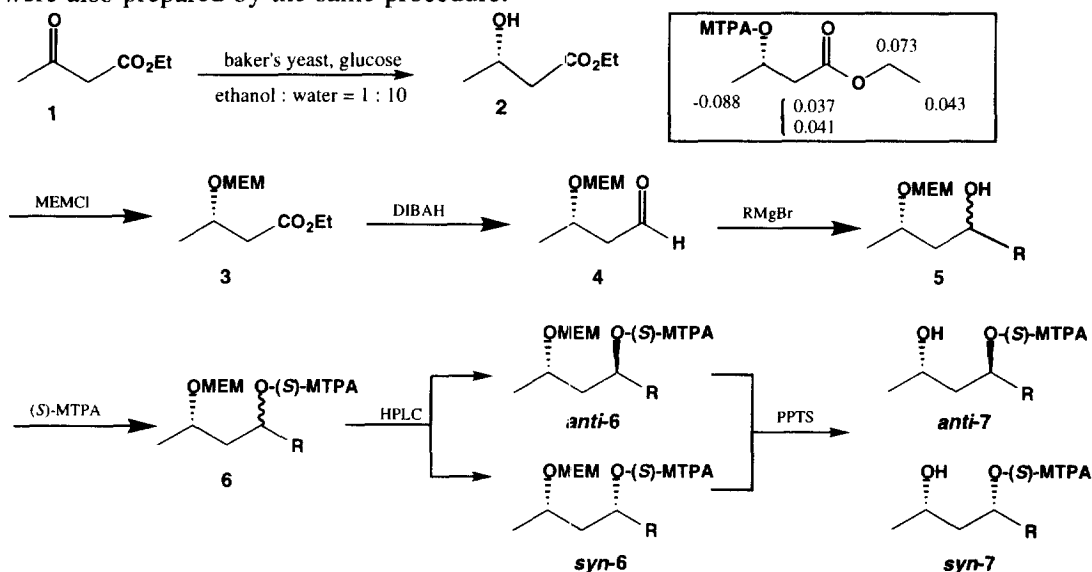
Absolute configurations of linear 1,3-diols can be determined by NMR spectroscopy by means of the modified Mosher's method. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Alcohols; Configuration; NMR; Stereochemistry

The 1,3-diol system is frequently found in the structure of pharmaceutically active natural products, and many papers have currently appeared on enantioselective construction of the system. Determination of the absolute configuration of the 1,3-diols included in linear compounds, however, is extremely difficult except for some cases to which a few physical methods, *e.g.*, X-ray crystallography, are applicable. Although the exciton chirality method is a reliable physical method for this purpose, it is applicable only to *anti*-1,3-diols but not to *syn*-1,3-diols [1]. In this paper, we describe the utility of the modified Mosher's method [2] in determining the absolute configuration of linear 1,3-diols.

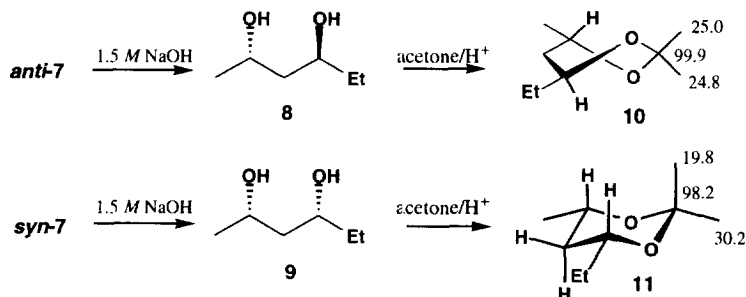
We at first started with the synthesis of the MTPA esters of several chiral 1,3-diols. Baker's yeast reduction [3] of 3-oxobutanoate afforded ethyl (*S*)-3-hydroxybutanoate (**2**, $[\alpha]_D^{+33.1^\circ}$ (*c* 2.30, CHCl_3)) [4], the absolute configuration of which was reconfirmed by the modified Mosher's method. The hydroxy group of **2** was protected with methoxyethoxy-methoxy (MEM) group and the resulting **3** was reduced with diisobutylaluminum hydride (DIBAH) to give (*S*)-3-MEMO-butanal (**4**). The aldehyde was treated with Grignard reagents (RMgBr ; R = ethyl, propyl, butyl, hexyl, octyl, 2-phenethyl) to afford (*S*)-2-MEMO-alcohols (**5**) as diastereomeric mixtures. The protected alcohols were esterified with

(*S*)-MTPA by the use of 2,4,6-trinitrochlorobenzene in dry pyridine [5]. The produced diastereomers (*anti*-6 and *syn*-6) were separated by HPLC (LiChrosorb Si 60, hexane : AcOEt = 4 : 1). Each diastereomer was deprotected with pyridinium *p*-toluenesulfonate (PPTS) in 2-butanone to give mono-MTPA ester (*anti*-7 and *syn*-7). The (*R*)-MTPA esters were also prepared by the same procedure.



In order to determine the relative configuration, each of the mono-(*S*)-MTPA esters ($R = \text{Et}$), *anti*-7 and *syn*-7, was hydrolyzed with 1.5 *M* NaOH/MeOH. The obtained 1,3-diols, **8** and **9**, were converted to acetonides, **10** and **11**. The ^{13}C NMR spectrum of the acetal **10** showed two acetal methyl signals at 24.8 and 25.0 ppm, and an acetal carbon signal at 99.9 ppm, while that of **11** revealed the acetal methyl signals at 19.8 and 30.3 ppm together with the acetal carbon signal at 98.2 ppm. Consequently, the relative configurations of the hydroxy groups in **8** and **9** were established to be *anti* and *syn*, respectively [6].

The CD spectrum of the di-*p*-bromobenzoate of *anti*-diol (**8**) showed a positive split Cotton effect, while that of *syn*-diol (**9**) di-*p*-bromobenzoate exhibited only a weak single negative Cotton effect (Figure 1). This confirmed that the CD method was useful for linear *anti*-diols,



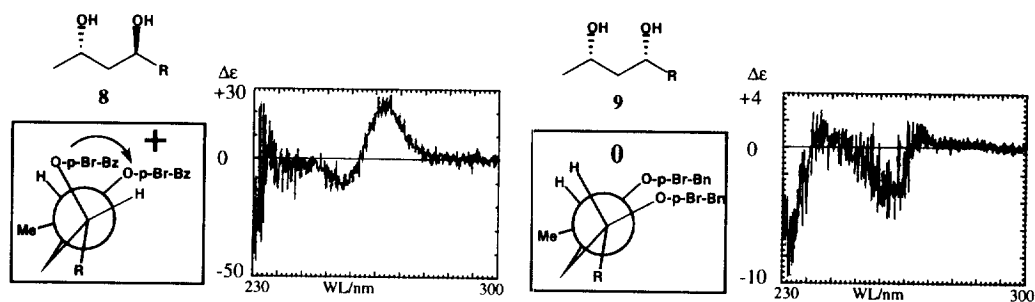


Figure 1. The CD spectra (EtOH) measured for the di-*p*-bromobenzoates of **8** (left) and **9** (right).

but incapable of determining the absolute configuration of *syn*-diols.

Here, we turned our attention to the modified Mosher's method. The $\Delta\delta$ values ($\Delta\delta = \delta_S\text{-MTPA} - \delta_R\text{-MTPA}$) obtained for *anti*-mono-MTPA esters as well as *syn*-mono-MTPA esters are shown in Figure 2. All the $\Delta\delta$ values are systematically distributed on the positive and negative sides of the MTPA plane, and the absolute configurations deduced from these results are correctly assigned. These findings indicate that the modified Mosher's method can be effectively applied to linear 1,3-diols.

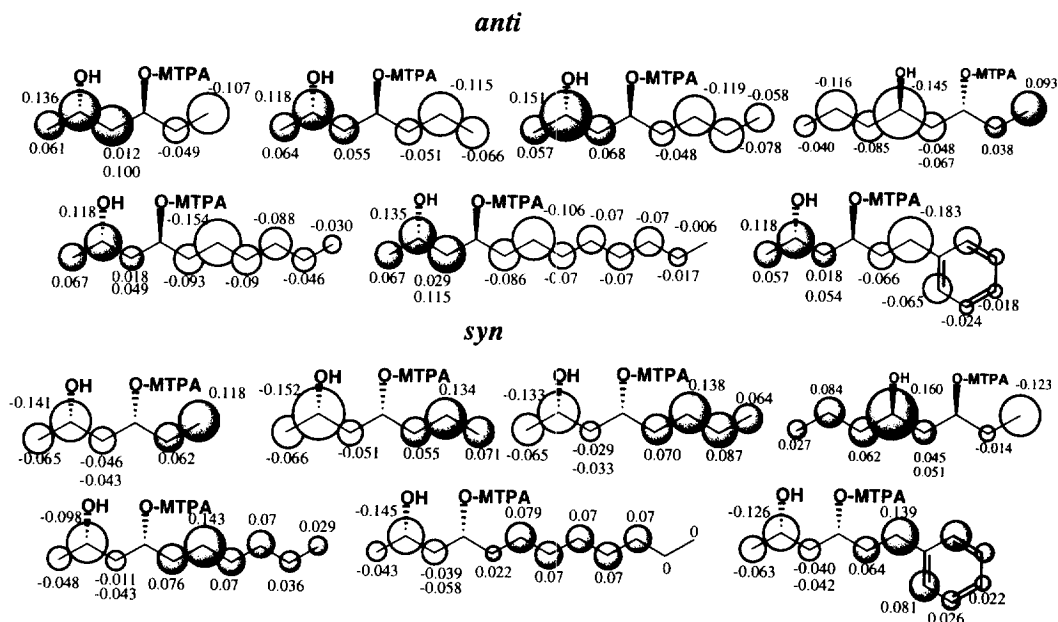


Figure 2. $\Delta\delta$ values obtained for the mono-MTPA esters of *anti*-diols (above) and *syn*-diols (below).

The present method can be used as a supplement to the CD method: When the CD spectrum of the 1,3-diol di-*p*-bromobenzoate (submilligram) in question shows a split Cotton

effect, the diol is in a 1,3-*anti* relation and the absolute configuration is assignable [1] as in Figure 1. When the CD does not show a clear split Cotton effect, the diol sample (1-2 mg) is treated with one equivalent of (*R*)-MTPA [*Important Note: (R)-MTPA chloride yields (S)-MTPA ester!*], and the resulting mono-(*R*)-esters are separated chromatographically [7]. Mono-(*S*)-MTPA esters are also prepared, and the $\Delta\delta$ values of the protons are calculated to determine the absolute configuration of each hydroxy group in the 1,3-diol.

During the present work, we noticed an interesting behavior of the $\Delta\delta$ values of the MEM group involved in **6** (Figure 3). The $\Delta\delta$ values of *anti*- and *syn*-**6** (R = Bu) are illustrated in Figure 2. Inversion of the signs (from + to -) is observed in the MEM protons of *anti*-compound, while no such tendency is seen in the *syn*-compound. This indicates that the *anti*-compound exists in a U-shaped conformation [8], while the MEM group of the *syn*-compound is stretched out of the molecule. The presence of NOE between 4-H and 10-H supports the supposed conformation of the *anti*-compound.

Very recently, the absolute configuration determination of the 1,3-diols by using the di-MTPA-esters has been reported [9].

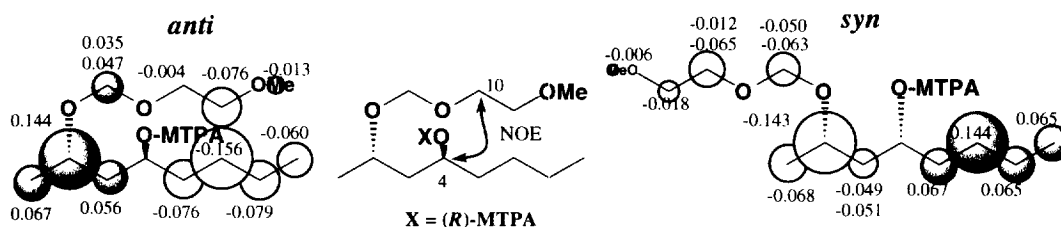


Figure 3. $\Delta\delta$ values obtained for the MEM derivatives of *anti*- (left) and *syn* (right)-2,4-octanediol MTPA esters. NOE is observed between 4-H and 10-H of the *anti*-compound (center).

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