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A Correlation of Configuration and ^{19}F-NMR Chemical Shifts of (R)-(+)-Mosher Esters of Chiral Cyclopentanediol Derivatives

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Esterification of chiral alcohols with (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid or its (S)-(−)-enantiomer (MTPA, Mosher acid) as homochiral auxiliaries affords the corresponding diastereomeric (R)- or (S)-Mosher esters, respectively. Analysis of the Mosher esters by ^{1}H-, ^{13}C-, or ^{19}F-NMR represents a useful method for the determination of the enantiomeric excess (e.e.) of chiral alcohols [1 – 9] on the basis of the nonequivalence of these spectra.

The application of ^{19}F-NMR for the determination of the e.e. using Mosher esters has some advantages. The fluorine signals are simple and located in an uncongested region. Owing to the nonequivalence of the spectra of diastereomeric esters the ^{19}F-NMR spectrum of a Mosher ester of a racemic alcohol consists of only two signals. The determination of the e.e. of an ester of enantiomerically pure Mosher acid and a chiral alcohol with one enriched enantiomer is of high accuracy. Systematic investigations on ^{19}F-NMR chemical shifts of the Mosher esters of various types of secondary alcohols, mostly in the presence of lanthanide shift reagents, have been reported [1, 2, 4, 6, 7].

During our work on lipase-catalyzed transesterifications of *meso*-cyclopentanediols in organic solvents [10, 11] affording the chiral cyclopentanediol monoacetates **1a – 6a** (Fig. 1) we used ^{19}F-NMR of the derived (R)-(+)-Mosher esters **1b – 6b** for the determination of the e.e. in the absence of lanthanide shift reagents. In general, the ^{19}F-NMR signals of the (R)-Mosher esters **1b – 5b** derived from the corresponding (S)-acetates show a downfield shift in comparison to the corresponding (R)-Mosher esters of the (R)-acetates (Table 1). This assignment was evidenced unambiguously by comparing the spectra of the (R)-Mosher esters of the racemic monoacetates **1a – 5a** with the spectra of the (R)-Mosher esters of the corresponding enantiomerically pure or enriched monoacetates of known configuration.

As in other series of chiral alcohols [2, 6] ^{19}F-NMR chemical shifts of the (R)-Mosher esters **1b – 6b** correlate with the absolute configuration of the chiral alcohols **1a – 6a**. This result can be explained by the proposed configuration-correlation model [2] which leads to nonequivalence of the CF_3 resonances in the diastereomers **1b – 6b** and in the diastereomers with (R)-Mosher acid of **ent-1a – ent-6a** due to an anisotropic deshielding of the CF_3 substituent. In the series of the cyclopentanediol monoacetates **1a – 6a** it should be possible on the basis of this correlation to predict the absolute configuration of a chiral alcohol of this type by measurement of its ^{19}F-NMR spectrum of the corresponding (R)-Mosher ester without addition of a lanthanide shift reagent.

An increase of Δδ was observed by substituting the double bond of **1b** by an epoxy, cyclopropyl, or isopropyli-

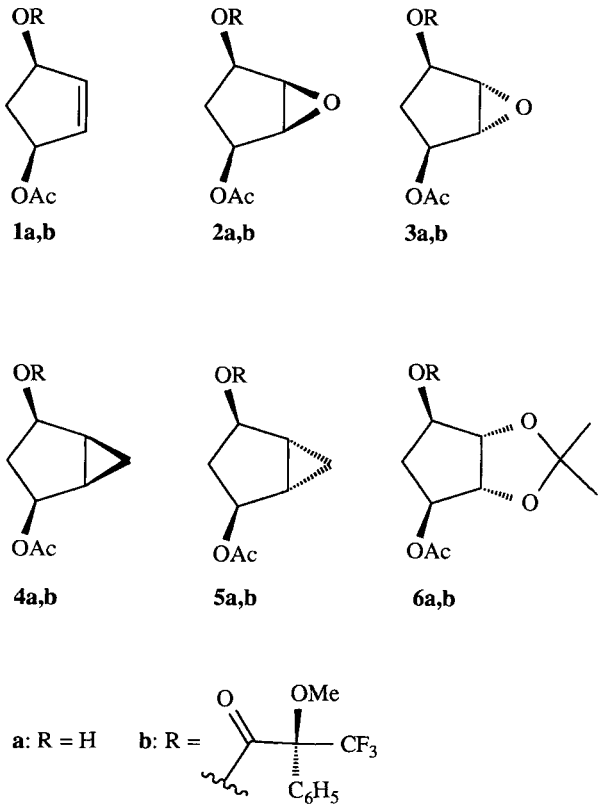

Fig. 1 Chiral cyclopentanediol derivatives and their corresponding Mosher esters

Table 1 ^{19}F-NMR Chemical Shifts[a] of the Mosher Esters **1b–6b**

Mosher ester	δ of the (S)-acetate	δ of the (R)-acetate	Δδ
1b	−72.17	−72.24	0.07
2b	−72.31	−72.41	0.10
3b	−72.10	−72.20	0.10
4b	−72.18	−72.36	0.18
5b	−72.02	−72.27	0.25
6b	−72.04[b]	−72.16[b]	0.12

[a] $\delta(CFCl_3) = 0$ ppm
[b] The absolute configuration was assigned on the basis of the correlation found for **1b–5b**, because an enantiomerically pure or enriched derivative **6a** was not available

denedioxy group. A correlation between the chemical nature and/or the relative stereochemistry of the substituted derivatives **2b–6b** and their ^{19}F-NMR spectra has not been possible so far owing to missing data of further derivatives. The elongation of the acyl side-chain from acetyl (**1b**) up to octanoyl does not influence the ^{19}F-NMR spetra [10].

Experimental

^{19}F-NMR spectra were measured at 282 MHz on a Gemini 300 (Varian) instrument or at 376 MHz on an MSL 400 (Bruker) instrument in $CDCl_3$ with $CFCl_3$ as internal standard.

Preparation of the (R)-(+)-Mosher esters **1b–6b**

A solution of (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (702 mg, 3.0 mmol) in dry dichloromethane (10 ml) was treated with 1,3-dicyclohexylcarbodiimide (310 mg, 1.5 mmol) and stirred at room temperature for 15 min. An aliquot (1 ml) of the resulting suspension was added to a solution of the corresponding chiral alcohol **1a–6a** (0.05 mmol), 4-dimethylaminopyridine (12 mg, 0.1 mmol) in dry dichloromethane (1 ml) and triethylamine (0.2 ml). After complete conversion to the Mosher esters **1b–6b** (TLC control, ≈ 2 h) the suspension was filtered and diluted with diethyl ether (5 ml). The filtrate was washed first with a 1*N* aqueous solution of sodium bicarbonate (5 ml) and then twice with water (5 ml). The organic phase was dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure. The residue was dissolved in diethyl ether (5 ml) and filtered again. The filtrate was evaporated to dryness and subjected to NMR analysis without further purification.

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