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CFTA, a new efficient agent for determination of absolute configurations of chiral secondary alcohols

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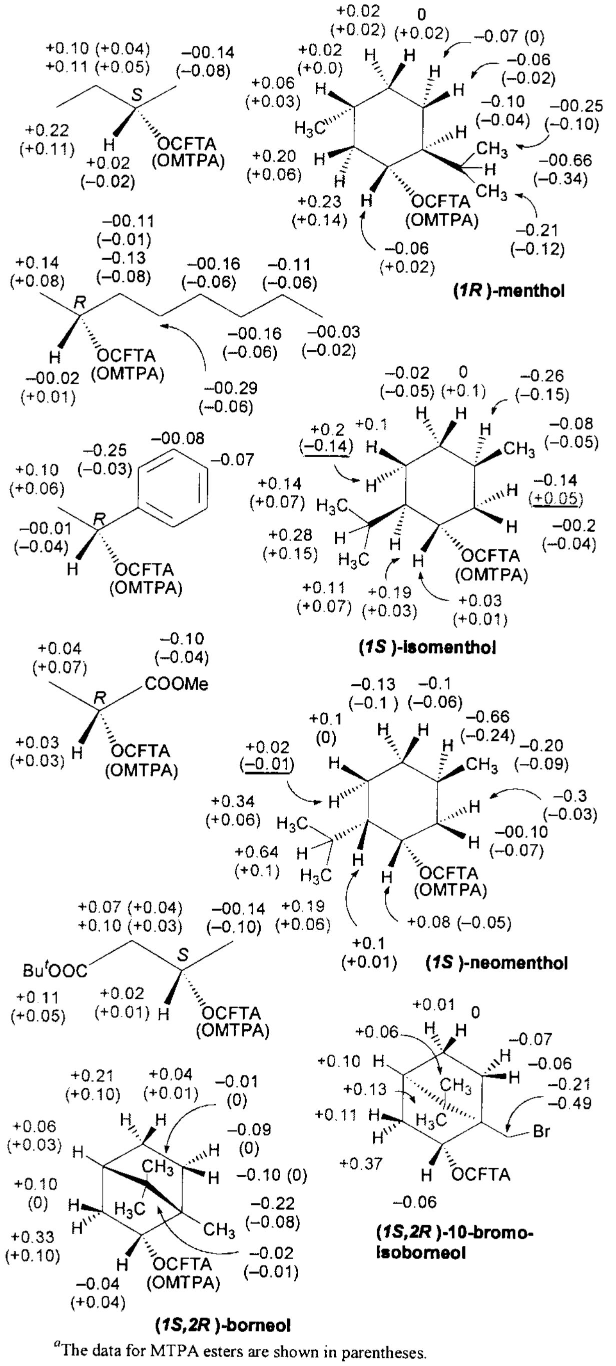
The CFTA method using α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA) can be reliable in assigning absolute configurations of chiral secondary alcohols based on both ^{1}H and ^{19}F NMR spectroscopy, and the most stable and most predominant conformer of the CFTA esters that can explain the ^{1}H and ^{19}F NMR data were supported by X-ray analysis and *ab initio* calculations.

Recent advances in enantioselective synthesis have produced an increasing demand for convenient and reliable techniques for assigning the absolute configuration of chiral molecules. A number of methods using chiral derivatizing agents (CDAs), such as α-methoxyarylacetic acids and α-methoxy-α-trifluoromethylphenylacetic acid (MTPA, Mosher's agent) by ^{1}H NMR spectroscopy have been developed for this purpose.[1] Among them, the well known modified Mosher method[2] using MTPA is one of the most reliable and widely applicable techniques to general secondary alcohols except sterically hindered ones. On the other hand, fluorine-containing CDAs are very useful with respect both to general applicability and convenience for the ee determination.[1c] In this case, the ^{19}F NMR spectroscopy is particularly useful because the shift differences are usually larger than those in the ^{1}H NMR spectra and there is seldom an overlap of signals. However, the ^{19}F-chemical shifts observed with MTPA[2] and fluorinated CDAs[3] can not be used for configuration determination because no general trend is observed. In the course of our continuing research to improve the utility of CDAs,[4] we have developed α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA).[5] This agent far surpasses the capabilities of MTPA with respect to both reactivity and signal resolution ability. We report here, that the ^{19}F NMR-based CFTA method is promising for the determination of absolute configuration of chiral secondary alcohols. In addition, the CFTA method using ^{1}H NMR is not only of higher reliability but also of broader applicability compared to the modified Mosher method.

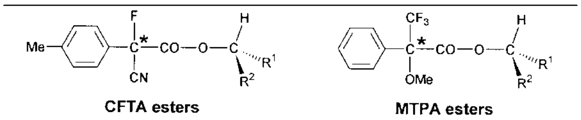
By a procedure similar to that used in the modified Mosher method,[2] we obtained the chemical shift difference, $\Delta\delta_H$ ($\delta_S - \delta_R$), for the corresponding protons in the diastereomeric (*S*)- and (*R*)-CFTA esters prepared from ten chiral secondary alcohols with known absolute configurations (Fig. 1). The results are as follows: (i) For all CFTA esters examined, the magnitude of $\Delta\delta_H$ was larger than that of the MTPA esters.[6] (ii) The signs of $\Delta\delta_H$ are distributed symmetrically with respect to the plane containing the carbinyl proton and the ester carbonyl (designated as the CFTA plane, Scheme 1). The $\Delta\delta_H$ values on the left side of the CFTA plane are positive and those on the right side negative. (iii) One of the most striking features of the CFTA method can be seen for the results for isomenthol. The signs of $\Delta\delta_H$ for the CFTA esters followed a regular plus order, while those for the MTPA esters did not. (iv) Another feature of the CFTA method can be seen for the application to 10-bromoisoborneol.[7] The CFTA esters were obtained, while the MTPA esters of this alcohol were not. These results validate the



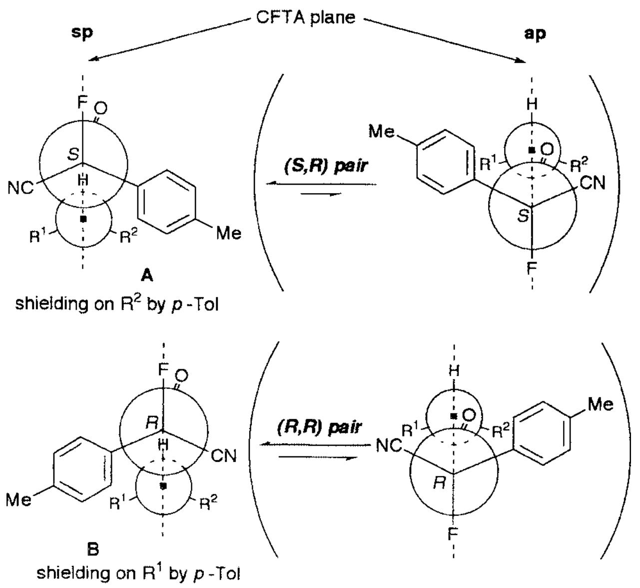
^{a}The data for MTPA esters are shown in parentheses.

Fig. 1 $\Delta\delta_H$ values obtained for the CFTA and MTPA esters^a [$\Delta\delta_H$/ppm = $\delta_S - \delta_R$].

Table 1 $\Delta\delta_F$ values obtained for the CFTA and MTPA esters



R¹	R²	$\Delta\delta_F$/ppm = $\delta_{SR} - \delta_{RR}$ or $\delta_{RS} - \delta_{SS}$	
		CFTA ester	MTPA ester
Me	Et	+0.08	+0.00
Me	Hex	+0.32	−0.05
Me	Ph	+0.87	−0.20
Me	COOMe	+1.28	−0.48
Me	CH_2COOBu^t	+0.59	+0.01
Bornyl		+0.74	+0.10
10-Bromoisobornyl		+0.92	—
Menthyl		+0.59	−0.11
Isomenthyl		+0.11	+0.02
Neomenthyl		+0.79	+0.22



Scheme 1

usefulness of the CFTA method to elucidate the absolute configuration of the secondary alcohols. Owing to the larger and more predictable signs of the $\Delta\delta_H$ values, as well as the higher reactivity of CFTA chloride compared to MTPA chloride, the CFTA method based on ^1H NMR spectroscopy should be more widely applicable than the modified Mosher procedure using MTPA esters.

In addition to the satisfactory results in ^1H NMR, the ^{19}F NMR-based CFTA method is promising. By a procedure similar to that used in the MTPA method,[2] we obtained the chemical shift difference, $\Delta\delta_F$ ($\delta_{SR} - \delta_{RR}$ or $\delta_{RS} - \delta_{SS}$)[8] in the diastereomeric (*S*)- and (*R*)-CFTA esters (Table 1). The larger $\Delta\delta_F$ values of the CFTA esters compared with the MTPA esters showed correlations to the absolute configuration of the alcohols. In contrast, no consistent correlation was found with the MTPA esters.

The relationship between the sign of $\Delta\delta_H$ and absolute configuration observed for the CFTA esters can be explained by the correlation model[1d,e,2] depicted in Scheme 1. In the model, the C–F is *synperiplanar* (sp) to the C=O bond, to which the carbinyl C–H is *syn*. The sp conformer was seen by the X-ray structure of (*R*)-CFTA ester of (1*S*)-neomenthol.[9] The signals due to the substituents that confront the aromatic ring (R² and R¹ groups in the diastereomers A and B, respectively) are always shifted upfield by the aromatic ring. Accordingly, the $\Delta\delta_H$ values for each proton in the R¹ group should be plus and those in the R² group minus. This model was supported by *ab initio* calculations [GAUSSIAN 98, RHF/6-31+G(d)] on the ground state geometry and energy of the diastereomeric pair of (*R*)-α-cyano-α-fluorophenylacetic acid (CFPA)[4] esters of (1*S*)- and (1*R*)-menthol.[10] Two predominant rotamers regarding the C_α–CO bond were found: one is the sp described above and the other is *antiperiplanar* (ap) with the C–F and C=O bonds. Calculations predicted a preference of the sp rotamers that can explain the signs of $\Delta\delta_H$ over the ap ones by *ca.* 0.94 and 0.55 kcal mol^{-1} for (*R*,*S*)- and (*R*,*R*)-esters, respectively. The signs of $\Delta\delta_F$ can be explained on the basis of the calculated chemical shifts of ^{19}F nuclei in the two rotamers[11] and the conformational bias between these. Since the observed chemical shifts were averaged between the sp and the ap, and the conformational equilibrium is more biased to the sp in the (*R*,*S*) ester than in the (*R*,*R*) ester, the ^{19}F signal in the (*R*,*S*) ester is expected to appear at lower field than that in the (*R*,*R*) ester, as observed.

In order to ensure the reliability of our method and to extend the range of applications, further investigations are currently underway.

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Notes and references

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6 The magnitude of $\Delta\delta_H$ of the CFTA esters was similar to that of the methoxyphenylacetic acid esters (MPA esters).[1f] However, MPA chloride did not react with 10-bromoisoborneol.

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8 The esters of (*S*)-acids with (*R*)-alcohols are designated *SR* and those of (*R*)-acids with (*R*)-alcohols are designated *RR*.

9 *Crystal data* for the (*R*)-CFTA ester of (1*S*)-neomenthol: $C_{20}H_{26}NO_2F$, M = 331.43, colorless, crystal size = 0.01 × 0.02 × 0.03 mm, triclinic, space group $P1$ (no. 1), a = 8.739(9), b = 9.404(9), c = 6.411(8) Å, α = 103.23(8), β = 97.33(9), γ = 111.00(8), V = 465(1) Å^3, Z = 1, D_c = 1.181 g cm^{-3}, no. of measured unique reflections = 2143 (2θ = 55°), T = 150 K, Mo-Kα radiation (λ = 0.71069 Å), Full-matrix least squares (teXan), R = 0.061 for 1570 observed F_o data [$I_o > 4.10\sigma(I_o)$], R_w = 0.062, GOF = 2.01, $\Delta\rho_{max}$ = 0.22 e Å^{-3}. At least one of the methyl hydrogens was located using a difference Fourier map and then the others were calculated geometrically on the basis of the observed hydrogen atoms. CCDC 182/1586. See http://www.rsc.org/suppdata/cc/b0/b001962n/ for crystallographic files in .cif format.

10 The tolyl group of CFTA was replaced by a phenyl group to reduce the number of atoms. The relative configuration of the (*R*,*S*) diastereomer is the same as that of the (*S*,*R*) diastereomer.

11 The ^{19}F chemical shifts of the two rotamers in each diastereomeric ester were calculated using GAUSSIAN 98 on the calculated structures described above: δ_F (δ_{CFCl_3} = 0) − 128.59 (sp) and −145.33 (ap) for the (*R*,*S*) ester; −133.05 (sp) and −146.47 (ap) for the (*R*,*R*) ester.