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Journal of Fluorine Chemistry 84 (1997) 19–23

JOURNAL OF FLUORINE CHEMISTRY

Study for the determination of the absolute configuration of fluoromethylated secondary alcohols by the modified Mosher method

Ling Xiao [a], Takashi Yamazaki [a], Tomoya Kitazume [a,*], Tetsuo Yonezawa [b], Yoshitake Sakamoto [b], Kouji Nogawa [b]

[a] *Department of Bioengineering, Tokyo Institute of Technology, Nagatsuta, Midori-ku Yokohama 226, Japan*
[b] *Department of Research and Development, Morita Chemical Industries Co. Ltd., Higasi-mikuni, Yadogawa-ku, Osaka 532, Japan*

Received 6 September 1996; accepted 15 February 1997

Abstract

Application of the modified Mosher method using high-field FT ^{1}H NMR to the 2-methoxy-2-phenyl-2-trifluoromethyl acetic acid (MTPA) derivatives of fluorinated secondary alcohols indicates that this method may be generally used to determine the absolute configurations of these materials. © 1997 Elsevier Science S.A.

Keywords: Fluorinated secondary alcohols; Absolute configuration

1. Introduction

One objective of research in fluorine chemistry, required to support applications in fluorine analogs of bioactive [1] and/or functionalized materials [2], is the development of methodology suitable for determination of the absolute configuration. There are a few physical methods, e.g. the exciton chirality method [3] and X-ray crystallography, however they have some limitations. Recently, in hydrocarbon chemistry, Kakisawa and coworkers have reported that a modification of Mosher's method is useful to elucidate the absolute configuration of secondary alcohols [4].

Accordingly, we have devoted our attention to application of the modified Mosher method to fluorinated secondary alcohols possessing a monofluoro-, difluoro- and/or trifluoromethyl group to determine the absolute configuration.

2. Results and discussion

Recently, Kakisawa and coworkers [4] have revealed that the high-field FT NMR application of Mosher's method is very convenient to elucidate the absolute configuration of chiral secondary alcohols using high-field ^{1}H NMR spectroscopy. Owing to the diamagnetic effect of the benzene ring, the $H_{A,B,C}$ NMR signals of the (*R*)-MTPA ester should appear upfield relative to those of the (*S*)-MTPA ester (MTPA is the 2-methoxy-2-phenyl-2-trifluoromethyl acetyl unit). When $\Delta\delta = \delta_S - \delta_R$, protons on the right side of the MTPA plane (Fig. 1) must have positive values ($\Delta\delta > 0$) and protons on the left side of the plane must have negative values ($\Delta\delta < 0$). This is illustrated in Fig. 2 [4].

In the references by Kakisawa and coworkers [4], when the following conditions (1–4) are all satisfied, the model shown in Fig. 1 will indicate the correct absolute configuration of the compound. The conditions can be extended as follows. (1) Assign as many proton signals as possible with

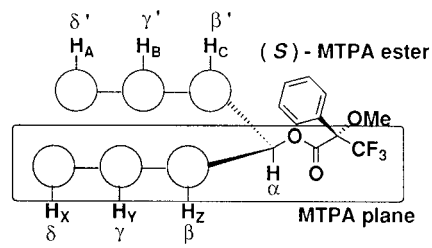


Fig. 1. MTPA plane of an MTPA ester. $H_{A,B,C}$ and $H_{X,Y,Z}$ are on the left and right sides of the plane respectively.

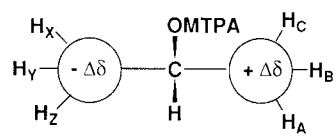


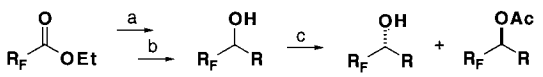
Fig. 2. Model used to determine the absolute configurations of secondary alcohols.

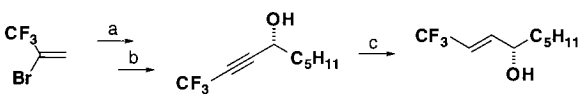
* Corresponding author.

PII S0022-1139(97)00026-2

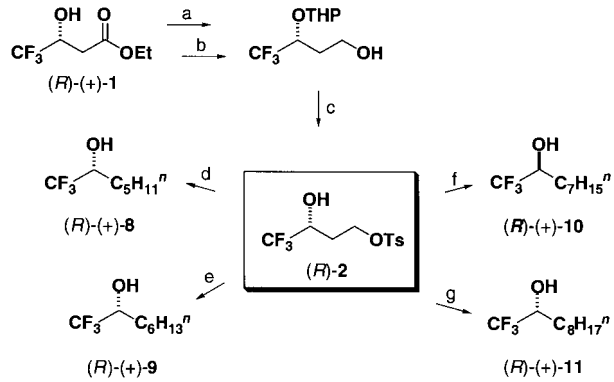
respect to each of the (*R*)- and (*S*)-MTPA esters. (2) Obtain $\Delta\delta$ values for the protons. (3) Put the protons with positive $\Delta\delta$ on the right side and those with negative $\Delta\delta$ on the left side of the model shown in Fig. 1. (4) Construct a molecular model of the compound in question and confirm that all the assigned protons with positive and negative $\Delta\delta$ values are actually found on the right and left sides of the MTPA plane respectively. This methodology is widely accepted to apply to elucidation of the absolute stereochemistries of various types of materials [5].

For the purpose of confirming whether the chemical shift behaviors of the protons of fluoromethylated materials actually accord with Kakisawa's rule (new Mosher method), fluoromethylated 2-alkanols (**4**–**21**), the absolute configurations of which are known, were examined. At first, we prepared various kinds of fluorinated 2-alkanols using the following procedures: (1) (+)-1,1,1-trifluoro-2-alkanols (compounds **4**–**11**) were prepared by asymmetric hydrolysis [6,7]; (2) other types of optically active 1,1,1-trifluoroalkanol derivatives (compounds **12**–**17**) were prepared by reported synthetic procedures [6,8,9]; (3) 1-fluoro- and 1,1-difluoro-2-alkanols (compounds **18**–**21**) were also prepared by known synthetic procedures [10].





The absolute stereochemistries of the prepared trifluoromethylated alkanols **4**–**17**, except compounds **8,9,10**, are already determined from those of the synthetic intermediates (*R*)-(+)-ethyl 4,4,4-trifluoro-3-hydroxybutanoate (**1**) and *S*-(−)-trifluoropropene oxide (**3**) which were confirmed by X-ray analysis [6–8,10–14]. We established the absolute configurations of optically active compounds **8,9,10** by synthesis from (*R*)-**2** as shown in Scheme 1. Further, the absolute configurations of trifluorinated alkanols (**4,5,6,7**), and monofluoro- and difluoromethylated alkanols (**18**–**21**) are known [6,10].



Scheme 1. (a) DHP, CH_2Cl_2; (b) $LiAH_4$, Et_2O; (c) TsCl, pyridine; (d) *n*-PrMgBr, Et_2O; (e) *n*-BuMgBr, Et_2O; (f) n-$C_5H_{11}MgBr$, Et_2O; (g) $(n$-$C_6H_{13})_2CuLi$, Et_2O.

(*R*)- and (*S*)-MTPA derivatives of fluorinated 2-alkanols were prepared by treatment of the corresponding optically active 2-alkanols with (*R*)- and (*S*)-2-methoxy-2-phenyl-2-trifluoromethyl acetic acid in the presence of *N,N′*-dicyclohexyl-carbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in dichloromethane (CH_2Cl_2). The $\Delta\delta$ values ($\delta_S - \delta_R$) obtained for these complexes are summarized in Figs. 3–5.

It is evident from the figures that protons with $\Delta\delta > 0$ are located on the right side of the MTPA plane, while those oriented on the left side of MTPA plane have $\Delta\delta < 0$. Also, $\Delta\delta$ values are almost proportional to the distance between the protons and the MTPA moiety. In Fig. 1, $\Delta\delta = \delta_S - \delta_R$ obtained from (*R*)- and (*S*)-MTPA derivatives of (+)-trifluorinated 2-alkanols is $\Delta\delta > 0$. These results suggest that the absolute configuration of all (+)-trifluorinated 2-alkan-

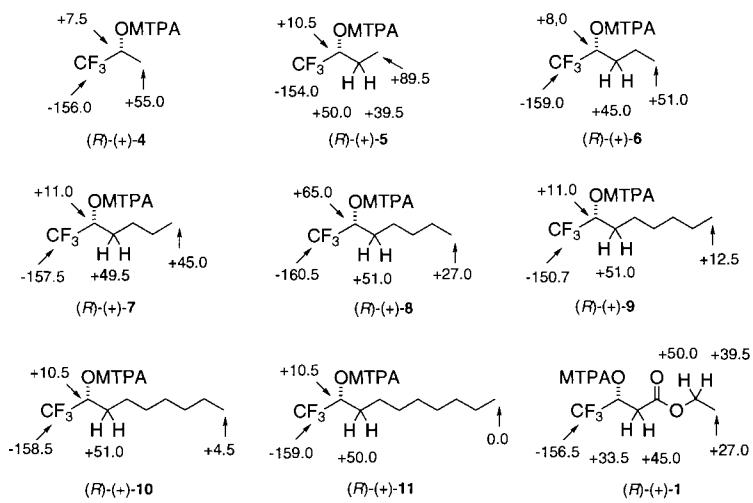


Fig. 3. $\Delta\delta$ ($\delta_S - \delta_R$) values obtained for the MTPA esters of (*R*)-(+)-trifluoromethylated 2-alkanols. $\Delta\delta$ values are expressed in hertz (500 MHz).

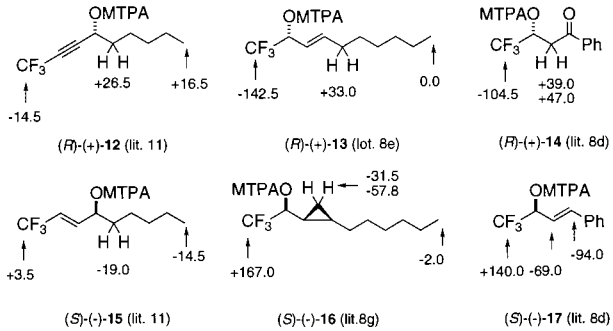


Fig. 4. $\Delta\delta$ ($\delta_S - \delta_R$) values obtained for the MTPA esters of trifluoromethylated alkanols. $\Delta\delta$ values are expressed in hertz (500 MHz). (*R*)-(+)-**12** [9], (*R*)-(+)-**13** [8], (*R*)-(+)-**14** [6], (*S*)-(−)-**15** [9], (*S*)-(−)-**16** [12], (*S*)-(−)-**17** [6].

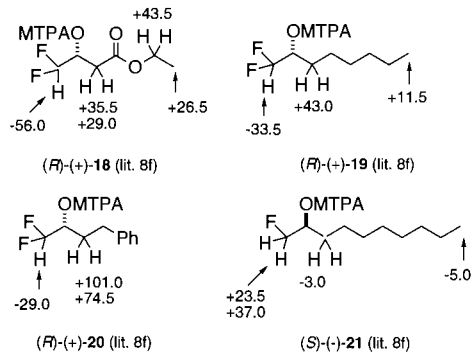


Fig. 5. $\Delta\delta$ ($\delta_S - \delta_R$) values obtained for the MTPA esters of (*S*)-(−)-monofluoromethylated 2-alkanols and (*R*)-(+)-difluoromethylated 2-alkanol. $\Delta\delta$ values are expressed in hertz (500 MHz). (*R*)-(+)-**18** [10], (*R*)-(+)-**19** [10], (*R*)-(+)-**20** [10], (*S*)-(−)-**21** [10].

ols shown in Fig. 3 is the *R*-configuration from the model indicated in Fig. 2. Furthermore, $\Delta\delta$ values obtained for the (+)- or (-)-trifluorinated 2-alkanols (**12**–**17**) containing the functionalized group (carbon–carbon double bond, cyclopropyl or carbonyl group) shown in Fig. 4, are in good agreement with the validity of the present methodology. For 1,1,1-trifluorinated 2-alkanols, as for non-fluorinated secondary alcohols.

In the next step, we examined the validity of this rule for other types of fluoromethylated compounds, (*R*)-(+)-1,1-difluoro-2-octanol (**18**), (*R*)-(+)-1,1-difluoro-2-decanol (**19**), (*R*)-(+)-1,1-difluoro-4-phenyl-2-butanol (**20**) and (*S*)-(−)-1-fluoro-2-decanol (**21**), the absolute configurations of which are known. Based on the comparison with Fig. 2 and $\Delta\delta$ values in Fig. 5, the absolute configuration of samples with $\Delta\delta > 0$ is the *R*-enantiomer.

In conclusion, the new methodology is also valid for determination of the absolute configuration of fluoromethylated alkanols.

3. Experimental details

3.1. General

All commercially available reagents were used without further purification. Chemical shifts of ^{1}H (500 MHz) and ^{13}C NMR spectra were recorded in ppm (δ) downfield from the following internal standards (Me_4Si, δ 0.00, or $CHCl_3$, δ 7.24). The ^{19}F (470 MHz) NMR spectra were recorded in ppm downfield from external trifluoroacetic acid in $CDCl_3$ using a VXR 500 instrument. Yields quoted are those of the products actually isolated.

3.2. Typical procedure for chloroacetate

3.2.1. 1,1,1-trifluoro-2-butyl chloroacetate [7]

(a) Preparation of 1,1,1-trifluoro-2-butanol. To a mixture solution of ethyl trifluoroacetate (460 g, 3.24 mol) and diethyl ether (1.5 l), the Grignard reagent derived from magnesium (87.5 g, 3.6 mol), ethyl bromide (400 g, 3.6 mol) in diethyl ether (1 l) was added slowly (more than 4 h) with cooling with ice-water under a nitrogen atmosphere. The whole mixture was stirred at room temperature for 30 min, and then the mixture was poured into a mixture of 12 N HCl (500 ml) and ice (700 g). Oily materials were extracted with diethyl ether. The extract was washed with saturated $NaHCO_3$ solution, and brine. On removal of the solvent, the crude of 1,1,1-trifluoro-2-butanone was obtained. Into a mixture solution of the above crude of 1,1,1-trifluoro-2-butanone, diethyl ether (3 l) and water (100 ml), a mixture solution of $NaBH_4$ (30.7 g, 0.81 mol) and water (150 ml) was added slowly (more than 3 h) below 20 °C, and the whole was stirred overnight at room temperature. Oily materials were extracted with diethyl ether. On removal of the solvent, distillation gave 1,1,1-trifluoro-2-butanol in 59% yield, bp 84 °C.

(b) Preparation of 1,1,1-trifluoro-2-butyl chloroacetate. To a mixture of 1,1,1-trifluoro-2-butanol (263.6 g, 1.9 mol) and chloroacetyl chloride (282 g, 2.5 mol) in CH_2Cl_2 (1.8 l), pyridine (237 g, 3 mol) was added for 1.5 h at 5–10 °C. After finishing the reaction by checking with gas chromatography, the mixture was poured into a mixture of 12 N HCl (400 ml) and ice (500 g). Oily materials were separated, and then were washed with saturated $NaHCO_3$ solution, and brine. On removal of the solvent, distillation gave 1,1,1-trifluoro-2-butyl chloroacetate in 93% yield (370 g, 66 °C/32 mm Hg).

Other chloroacetates [7], such as 1,1,1-trifluoro-2-pentyl chloroacetate, 1,1,1-trifluoro-2-hexyl chloroacetate, 1,1,1-trifluoro-2-heptyl chloroacetate and 1,1,1-trifluoro-2-nonyl chloroacetate, were also obtained in the same procedure using pentyl-, hexyl-, heptyl- or nonyl-magnesium bromide.

3.2.2. Typical procedure of asymmetric hydrolysis

A mixture of 1,1,1-trifluoro-2-octylchloroacetate (50 g), lipase MY (0.02 g, *Candida rugosa*, Meito Sangyo Co. Ltd.) in buffer solution (made from 0.5 M KH_2PO_4 (250 ml) and 0.5 M NaOH (145 ml)) was stirred for 6 h at 38 °C. After quenching with 1 N HCl, organic materials were extracted with methylene chloride (500 ml), and then the extract was dried over $MgSO_4$. Removal of the solvent and distillation gave (*R*)-(+)-1,1,1-trifluoro-2-octanol **9** (13.1 g, bp 55–56 °C/20 mm Hg, >98% ee) [6,7].

3.2.3. 1,1,1-Trifluoro-2-nonyn-4-ol [9]

To a solution of lithium diisopropylamine (44 mmol) in THF (40 ml) was added dropwise a precooled (−78 °C) solution of 2-bromo-3,3,3-trifluoropropene (3.5 g, 20 mmol) in THF (20 ml) at −78 °C. After stirring for 5 min, *n*-$C_5H_{11}CHO$ (2.5 ml, 24 mmol) was added to this solution and the whole was stirred for 30 min. The reaction mixture was quenched with 1 N HCl aq (100 ml) and extracted with AcOEt three times. The organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel to afford 3.96 g (19.8 mmol) of 1,1,1-trifluoro-2-nonyn-4-ol in 93% yield, bp 100 °C/2 mm Hg. ^{1}H NMR ($CDCl_3$): δ 0.8–1.0 (3 H, m), 1.2–2.0 (8 H, m), 2.6–3.0 (1 H, br), 4.454 (1 H, tq, J=6.69, 2.98 Hz). ^{13}C NMR ($CDCl_3$): δ 13.838, 22.411, 24.467, 31.202, 36.576 (q, J=1.22 Hz), 61.77 (q, J=1.48 Hz), 71.957 (q, J=52.88 Hz), 87.947 (q, J=6.30 Hz), 114.041 (q, J=257.15 Hz). ^{19}F NMR ($CDCl_3$): δ 28.4 (s) from ext. CF_3CO_2H. lR (neat) 3325 cm^{-1}.

3.2.4. (R)-1,1,1-Trifluoro-2-nonyn-4-ol [9]

To a 0.17 M solution of a racemic 1,1,1-trifluoro-2-nonyn-4-ol (4.03 mmol) in *n*-hexane (24 ml) were added vinyl acetate (8.10 ml, 97.4 mmol) and lipase PL (0.548 g, 49320 U; *Alcaligenes* sp. Meito Sangyo Co., Ltd., Japan), and the whole was stirred at 30 °C for 24 h. After removal of the residue by filtration and concentration of this solution, separation by silica gel column chromatography afforded an optically active (*S*)-1,1,1-trifluoro-2-nonyn-4-ol (yield 45%) and (*R*)-1,1,1-trifluoro-4-acetoxy-2-nonyn. (*R*)-1,1,1-trifluoro-2-nonyn-4-ol (>80% ee) was obtained by the hydrolysis of (*R*)-1,1,1-trifluoro-4-acetoxy-2-nonyn in the aq. NaOH (5%)–acetone system. (*S*)-1,1,1-trifluoro-2-nonyn-4-ol: $[\alpha]_D^{14}$ −4.1 (*c* 0.8, $CHCl_3$) (>99% ee). ^{1}H NMR ($CDCl_3$): δ 0.8–1.0 (3 H, m), 1.2–2.0 (8 H, m), 2.6–3.0 (1 H, br), 4.454 (1 H, tq, J=6.69, 2.98 Hz). ^{13}C NMR ($CDCl_3$): δ 13.838, 22.411, 24.467, 31.202, 36.576 (q, J=1.22 Hz), 61.77 (q, J=1.48 Hz), 71.957 (q, J=52.88 Hz), 87.947 (q, J=6.30 Hz), 114.041 (q, J=257.15 Hz). ^{19}F NMR ($CDCl_3$): δ 28.4 (s) from ext. CF_3CO_2H. IR (neat) 3325 cm^{-1}. (*R*)-1,1,1-trifluoro-4-acetoxy-2-nonyn. ^{1}H NMR ($CDCl_3$): δ 0.90 (3 H, t, J=6.84 Hz) 1.30–1.50 (6 H, m) 1.70–1.90 (2 H, m) 2.11 (3 H, s) 5.86 (1 H, tq, J=2.93, 5.86 Hz). ^{13}C NMR ($CDCl_3$): δ 13.80, 20.61, 22.32, 24.34, 31.05, 33.62, 62.48, 72.09 (q, J=53.0 Hz), 84.66 (q, J=6.4 Hz), 113.83 (q, J=258 Hz), 169.53. ^{19}F NMR ($CDCl_3$): δ 11.14 (d, J=3.05 Hz) from ext. C_6F_6. IR (neat) 1753 cm^{-1}. $[\alpha]_D^{15}$ +50.8 (*c* 0.7, $CHCl_3$) (81% ee).

3.2.5. (S)-1,1,1-Trifluoro-(E)-2-nonen-4-ol [9]

To a stirring solution of Red-Al (2.5 mmol) in toluene (3 ml) at −78 °C was added (*S*)-1,1,1-trifluoro-2-nonyn-4-ol (2.1 mmol). After 3 h of stirring at that temperature, the reaction was quenched with 1 N HCl (10 ml) and the usual work-up gave the crude olefin. After purification by silica gel column chromatography, (*S*)-1,1,1-trifluoro-(*E*)-2-nonen-4-ol was obtained in 79% yield.

*3.2.6. Preparation of compounds **8–10***

(*R*)-(+)-1,1,1-*Trifluoro*-2-*heptanol* (**8**). Into a solution of *n*-propyl magnesium bromide (1.5 mmol) in freshly dried diethyl ether (5 ml), was added *R*-tosylate **2** (1 mmol) [6] in diethyl ether (5 ml) slowly at −70 °C. After 1.5 h of stirring at that temperature, the mixture was warmed to room temperature, and the whole was stirred overnight at that temperature. The mixture was poured into water, and then the ethereal layer was separated. (*R*)-(+)-1,1,1-Trifluoro-2-heptanol **8** was purified by column chromatography on silica gel.

(*R*)-(+)-1,1,1-*Trifluoro*-2-*octanol* (**9**). In the above reaction, *n*-butyl magnesium bromide was used, and then worked up similarly. (*R*)-(+)-1,1,1-Trifluoro-2-octanol **9** was purified by column chromatography on silica gel.

(*R*)-(+)-1,1,1-*Trifluoro*-2-*nonanol* (**10**). In the above reaction, *n*-pentyl magnesium bromide was used, and then worked up similarly. (*R*)-(+)-1,1,1-Trifluoro-2-nonanol **10** was purified by column chromatography on silica gel.

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