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Application of (*S*)-trifluorolactic acid for chiral derivatizing agent

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Dedicated to Dr. Yoshiro Kobayashi on the occasion of his 75th birthday

Abstract

Optical purities of alcohols could be conveniently estimated by at least one of such analytical methods as GC, LC or ^{19}F-NMR after derivatization into the corresponding esters by reaction with chiral trifluorolactic acid. *O*-Alkylation of trifluorolactates was found to enhance the separation of isomers by GC and ^{19}F-NMR analyses.

Keywords: Trifluorolactic acid; Chiral derivatizing agent; Chiral alcohol; Optical purity; Diastereomer

1. Introduction

Recent increasing demands of chiral compounds in the fields of medicinals, electronic devices, and so on has led to the rapid development of a number of novel as well as versatile asymmetric synthetic methods (see, for example, [1]), which also strongly require appropriate analytical means for determination of optical purities of chiral products thus obtained. One of the easiest methods for this purpose would be GC and LC equipped with chiral fixed phase columns, but the setting of analytical conditions is intricate.

A new type of chiral derivatizing agents (CDA), α-cyano-α-fluorophenylacetic acid and α-cyano-α-fluoro-*p*-tolylacetic acid for ^{19}F-NMR analysis were reported by Takeuchi et al. [2–5], and the utility of α-(trifluoromethyl)-α-methoxypropionic acid was clarified by Yasuhara et al. for GC analysis [6]. Although many other CDAs are also commercially available and provide optical purity information by way of chromatographic or spectroscopic analyses [7–9], they are generally quite expensive and sometimes unstable for long storage. Additionally, some of them, for example MTPA, must be transformed to reactive forms before reaction with substrates [10].

On the other hand, as trifluorolactic acid (TFLA) has a hydroxyl group α to the carbonyl moiety, it might be possible to estimate optical purities of diastereomeric substrates by judicious modification of this specific site, even when good separation is not attained. Moreover, TFLA seems to be a good derivatizing agent because (i) ^{19}F-NMR, sensitive to subtle circumstantial changes, can be used, (ii) the resultant derivatives can be applied to GC analysis due to increased volatility by three fluorines, and (iii) this compound is readily accessible by several synthetic methods [11–17], among which resolution of racemic TFLA [13] and nitric acid oxidation of chiral trifluoropropene oxide [14–16] are excellent routes of choice. Chiral trifluoropropene oxide is also prepared through asymmetric reduction of 1-bromo-3,3,3-trifluro-2-propanone [17]. Furthermore, optically pure (*S*)-TFLA can be obtained through recrystallization twice from the ether–chloroform (1:50) system [14–16].

This article describes the investigation for the potential ability of TFLA as a chiral derivatizing agent for optically active chiral secondary alcohols.

2. Results and discussion

2.1. Esterification of (S)-TFLA with chiral secondary alcohols

When (*S*)-TFLA is used as CDA or resolving reagent of alcohols (**1**), esterification is desirable to readily proceed under mild conditions in quantitative yield. TFLA could not

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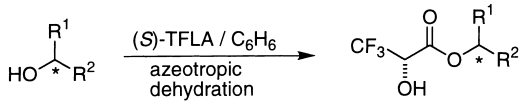
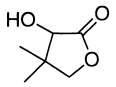
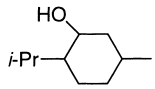


			Yield (%)
1a	$R^1 = CH_3$, $R^2 = CH_2CH_3$	**2a**	98
1b	$R^1 = CH_3$, $R^2 = (CH_2)_2CH_3$	**2b**	95
1c	$R^1 = CH_3$, $R^2 = (CH_2)_3CH_3$	**2c**	95
1d	$R^1 = CH_3$, $R^2 = (CH_2)_5CH_3$	**2d**	96
1e	$R^1 = CH_3$, $R^2 = (CH_2)_7CH_3$	**2e**	99
1f	$R^1 = CH_3$, $R^2 = Ph$	**2f**	99
1g	$R^1 = CH_3$, $R^2 = CH_2CO_2Et$	**2g**	95
1h	$R^1 = CH_3$, $R^2 = CH{=}CH_2$	**2h**	95
1i	$R^1 = CH{=}CH_2$, $R^2 = (CH_2)_4CH_3$	**2i**	90
1j	$R^1 = CH_2CH_3$, $R^2 = (CH_2)_2CH_3$	**2j**	93
1k	$R^1 = CF_3$, $R^2 = CH_2CH_3$	**2k**	98
1l	$R^1 = CF_3$, $R^2 = (CH_2)_2CH_3$	**2l**	95
1m	$R^1 = CF_3$, $R^2 = (CH_2)_3CH_3$	**2m**	93
1n	$R^1 = CF_3$, $R^2 = (CH_2)_5CH_3$	**2n**	92
1o	$R^1 = CF_3$, $R^2 = (CH_2)_7CH_3$	**2o**	98
1p	$R^1 = CH_2CH_3$, $R^2 = (CH_2)_4CH_3$	**2p**	92
1q	$R^1 = (CH_2)_2CH_3$, $R^2 = (CH_2)_5CH_3$	**2q**	99
1r	$R^1 = H$, $R^2 = CH(CH_3)CH_2CH_3$	**2r**	97
1s		**2s**	88
1t		**2t**	91

Scheme 1.

be derived in acid chloride form with thionyl chloride or phthaloyl dichloride, because the reaction procduces a complex mixture. Fortunately, as TFLA has relatively high acidity, TFLA is considered to behave as an acid catalyst for esterification. Actually, azeotropic dehydration from a mixture of (*S*)-TFLA and alcohols (**1**) readily proceeded to form the corresponding esters (**2**) using benzene or toluene as a solvent even without any additional acid catalysts such as *p*-toluenesulfonic acid or sulfuric acid (Scheme 1). In spite of the hydroxyl group at the chiral center, the self-condensation of TFLA affording the corresponding oligomers did not proceed at all under the esterification condition and even refluxing of benzene solution of TFLA in the presence of *p*-toluenesulfonic acid. No racemization was observed during the esterification procedure by GC analysis using a column modified with chiral stationary phase (CP-Cyclodex-β236M; GL Science).

On the other hand, since 2-acyloxy-3,3,3-trifluoropropionyl chloride derived from TFLA readily reacted with amines to form the corresponding amide with racemization, TFLA is unfavorable for CDAs for chiral amines.

2.2. Chromatographic separation of diastereomers of esters 2

As esters **2** have a trifluoromethyl group at α-position to carbonyl, their volatility is considered to be suitable for GC analysis. Actually, the retention times of **2** were no more than 20 min under general analytical conditions with TC-WAX (PEG-20M equivalent, strong-polar capillary column). In Table 1 are summarized such analytical results

Table 1
Gas chromatographic separation of diastereomeric ester **2**

Ester **2**	Separation index			GC conditions[a]	
	α[b]	k'[c]	Rs[d]	Initial temp. (°C)[e]	Program rate (°C min^{-1})
2a	1.063	9.337	1.637	70	0
2b	1.025	2.067	1.420	120	4
2c	1.000	3.246	0.000	120	4
2d	1.022	2.262	1.482	120	0
2e	1.033	7.892	1.568	140	0
2f	1.080	5.459	3.286	150	0
2g	1.152	12.03	1.921	140	1
2h	1.056	10.57	1.718	120	0
2i	1.056	9.912	1.761	120	0
2j	1.038	7.690	2.215	100	0
2k	1.671	14.70	10.440	80	1
2l	1.688	2.163	6.905	120	4
2m	1.728	1.728	3.724	120	4
2n	1.670	9.592	6.304	120	4
2o	1.506	8.667	8.110	140	1
2p	1.027	12.86	1.903	110	1
2q	1.000	6.902	0.000	120	4
2r	1.000	3.233	0.000	120	4
2s	1.000	15.26	0.000	120	4
2t	1.083	3.715	3.083	160	0

[a] TC-WAX (0.25 mm i.d.×30 m, GL Science, PEG-20M compatible capillary column) was used. Carrier: 70 ml/min (He); sprit ratio: 100:1.
[b] Separation factor.
[c] Capacity factor of latter fraction.
[d] Resolution.
[e] Each initial temperature was held for 10 min, and all final temperatures were controlled at 200°C except the cases where program rate was zero.

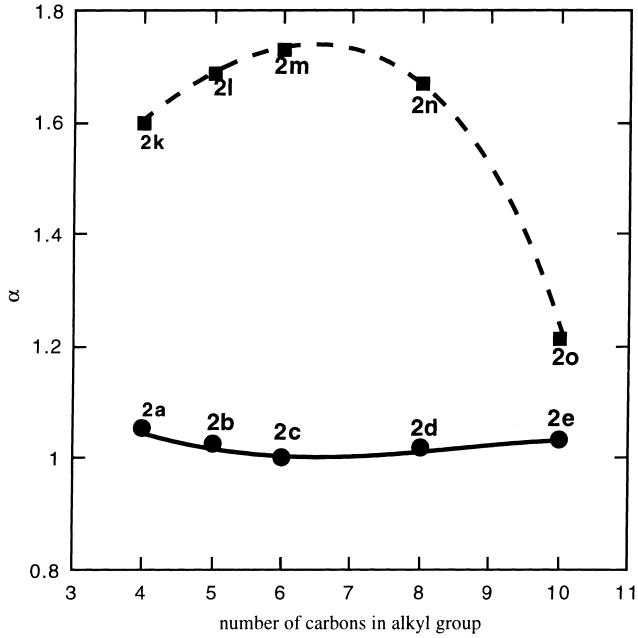


Fig. 1. Plots of separation factor (α) vs. alkyl carbon chain length of **2a–e** and **2k–o**. Normalized GC conditions: column, TC-WAX (0.25 mm i.d.×30 m, GL Science); carrier, 70 ml (He, split ratio, 100:1); initial temperature, 120°C was held for 10 min; program rate, 4°C/min; final temperature, 200°C.

as separation factor (α), capacity factor (k') of isomer with longer retention time and resolution (Rs>1.500 :base-line separation) as the analytical indication functions.

The relatively large resolutions of allylic esters **2h** and **2i** would be stemmed from the structural difference between alkyl and vinyl groups. Similarly, the large diastereomeric separation of **2g** might result from the polar terminal ethoxycarbonyl. In contrast, as the steric difference around the chiral center in the alkyl part between ester diastereomers is relatively small in the case of **2q** and **2r**, the diastereomeric separation did not occur.

Moreover, similar GC analysis of **2** was performed under normalized conditions. The plots between the carbon number in the alkyl part of esters (**2a–e**) and separation factors α had a minimum at n=6 (**2c**). On the contrary, the curve of α in similar plots for the esters bearing a trifluoromethyl group at the alkyl part (**2k–o**) had a maximum at n=6 (**2m**) (Fig. 1). This quite sharp contrast was considered not only due to the steric factor difference around chiral centers of alkyl parts, but also due to the polarity difference of the whole molecular structure.

In the LC analysis, the diastereomeric separation of **2** could not be observed using the reversed phase type column (ODS), but in half of the samples examined here, base-line separation (Rs>1.500) was observed by a silica gel column eluted with hexane–2-propanol (95:5). The analytical results are summarized in Table 2.

2.3. NMR spectroscopic separation of 2

^{19}F-NMR spectrometry is one of the most useful instrumental techniques for the analysis of optical purity when

Table 2
Diastereomeric separation of **2** using HPLC[a]

Ester **2**	Separation index			Flow rate (ml min^{-1})
	α[b]	RT[c] (min)	Rs[d]	
2a	1.000	4.180	0.000	9.0
2b	1.108	29.74	1.995	1.0
2c	1.037	4.730	1.029	6.0
2d	1.056	26.30	1.548	1.0
2e	1.059	4.560	1.617	6.0
2f	1.073	5.193	1.941	6.0
2g	1.058	6.353	1.544	9.0
2h	1.000	3.170	0.000	9.0
2i	1.062	9.700	1.038	3.0
2j	1.033	31.86	1.532	1.0
2k	1.000	27.19	0.000	3.0
2l	1.000	7.892	0.000	3.0
2m	1.090	4.520	1.905	9.0
2n	1.000	13.42	0.000	3.0
2o	1.133	14.21	2.001	3.0
2p	1.000	9.010	0.000	3.0
2q	1.076	3.666	1.709	9.0
2r	1.270	3.580	3.167	9.0
2s	1.069	27.35	1.564	3.0
2t	1.000	3.940	0.000	9.0

[a] Column: Inertsil SIL 100A (4.0 mm i.d.×250 mm, GL Science); eluent: *n*-hexane-2-propanol (95/5 [v/v]); charged sample: 5 μl (concentration=10 mg/1.0 ml).
[b] Separation factor.
[c] Retention time.
[d] Resolution.

Table 3
^{19}F-NMR shift difference of **2**[a]

Ester **2**	$\Delta\delta$ (Hz)
2a	1.69
2b	3.39
2c	2.26
2d	1.69
2e	2.26
2f	10.05
2g	3.67
2h	3.90
2i	2.15
2j	2.71
2k	1.81 (1.69)[b]
2l	1.75 (1.86)[b]
2m	2.03 (2.43)[b]
2n	1.98 (2.26)[b]
2o	2.15 (1.81)[b]
2p	2.37
2q	1.24
2r	3.67
2s	1.58
2t	6.27

[a] Hitachi R1200F (56.46 MHz) spectrometer was used. Solvent: $CDCl_3$.
[b] $\Delta\delta$ of CF_3 group at alcohol part of **2**.

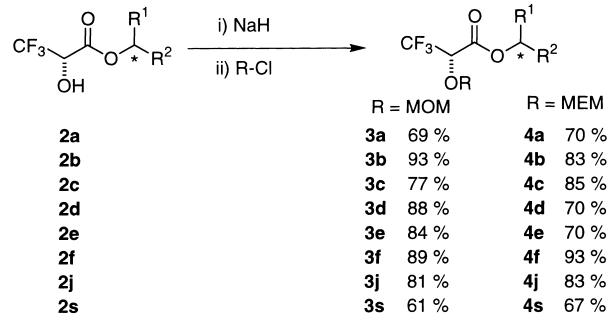
fluorine-containing CDAs are used. In particular, even a reaction mixture of derivatization step in a variety of common solvents can be directly used for the determination of the optical purity, since most substrates whose optical purities have to be determined do not have fluorines in the molecules. Although the CF_3 signal of the TFLA unit appears as a doublet in ^{19}F-NMR, the spectra of **2** showed clear base-line separated diastereomeric signals and gave highly precise quantification of optical purities even by a 56.46 MHz ^{19}F-NMR spectrometer (Table 3).

On the other hand, isolation of chiral derivatized samples is necessary for ^{1}H-NMR measurement. Additionally, as many signals originated from samples appear in the ^{1}H-NMR spectra, quantification of optical purities is significantly more complicated than in the case of ^{19}F-NMR. Although doublet methyl signals at 1-position of secondary alkyl moiety of **2a–h** appeared as diastereomerically separated patterns ($\Delta\delta$=8.00–14.40 Hz), quantification using ^{1}H-NMR was concluded to be available only for 2-alkanols but unfavorable for the other alcohols.

2.4. Improvement of diastereomeric separation by *O*-alkylation of 2

The results described above showed that TFLA, easy to be stored and to be used, can be utilized as a CDA for chiral secondary alcohols. However, in some cases diastereomerically separated signals or peaks of TFLA-based esters are not observed by GC, LC, ^{1}H-NMR or ^{19}F-NMR.

Fortunately, as esters **2** have a hydroxyl group at α-position to carbonyl of the acid part, it is thought that *O*-alkylation of hydroxyl group may favorably affect the resolution of diastereomeric peaks or signals. Methoxymethyl (MOM) and 2-methoxyethoxymethyl (MEM) chloride were selected as the alkylating reagents because of their high reactivity towards the hydroxyl group.



Scheme 2.

Derivatization to MOM and MEM ethers (**3**, **4**) was carried out through a Williamson type method in quantitative yield (Scheme 2). As esters **2** have an α-methine proton in TFLA unit, epimerization might occur. However, any racemization did not occur in these cases confirmed by GC and/or LC analyses using columns with chiral stationary phase.

In the GC analyses of **3** and **4**, most of the samples showed the base-line separated peaks. Especially, diastereomeric esters (**3b–e**, **4b–e**) from 2-alkanols showed base-line separation patterns with larger resolution values than those of non-*O*-alkylated esters **2**. On the contrary, the diastereomeric peaks were observed as a completely separated pattern in the cases of unsubstituted **2f**, but *O*-alkylation (**3f**, **4f**) resulted in a decrease in Rs values (Rs<1.500; overlapping pattern) (Table 4).

The plotting pattern of α values vs. carbon number of chiral alcohols in both *O*-MOM esters and *O*-MEM ester (**3a–e** and **4a–e**) showed a maximum value at 2-hexylesters, quite different from that of non-*O*-alkylated ester (**2a–e**) (see Figs. 2 and 1). These results suggested that *O*-alkylation of the original esters **2a–e** can change the separation mode in the GC column by masking the polar hydroxyl group. Thus, it was found that *O*-alkylation of **2** by MOM or MEM groups is effective for the enhancement of resolution of diastereomeric peak separation on the gas chromatogram in many cases.

On the ^{19}F-NMR analysis, the results for esters **3a–e** and **4a–e** showed the shift difference enhancement, while the resolutions became poorer by *O*-alkylation in the case of **3f–s** and **4f–s**. All of the separation patterns of **3** and **4** were clearly base-line separation and shift differences were large enough to determine optical purities of original alcohols (Table 5).

As acetal methylene signals of MOM and MEM groups are observed as singlet sometimes at relatively isolated shift position (typically, δ 4.2–5.0 ppm) in ^{1}H-NMR, it is expected that the methylene signals are available for quantification of optical purity. Although the $\Delta\delta$s of terminal

Table 4
Gas chromatographic separation of *O*-alkylated diastereomeric esters **3** and **4**

Ester **3** or **4**	Separation index			GC conditions[a]	
	α[b]	k'[c]	Rs[d]	Initial temp. (°C)[c]	Program rate (°C min^{-1})
3a	1.062	10.57	1.621	70	0
3b	1.041	9.662	1.635	80	1
3c	1.052	6.519	1.591	100	0
3d	1.039	5.991	1.684	120	4
3e	1.019	7.701	1.792	120	4
3f	1.002	49.40	1.448	60	1
3j	1.040	7.592	1.972	70	0
3s	1.000	8.982	0.000	120	0
4a	1.049	7.420	1.588	120	0
4b	1.026	8.258	1.566	120	4
4c	1.042	8.494	1.590	80	0
4d	1.062	6.275	1.880	130	0
4e	1.081	12.04	2.125	160	0
4f	1.003	16.34	1.471	60	5
4j	1.042	8.494	1.981	80	0
4s	1.000	17.06	0.000	120	4

[a] TC-WAX (0.25 mm i.d.×30 m, GL Science, PEG-20M compatible capillary column) was used. Carrier: 70 ml/min (He); sprit ratio: 100:1.
[b] Separation factor.
[c] Capacity factor of latter fraction.
[d] Resolution.
[e] Each initial temperature was held for 10 min, and all final temperatures were controlled at 200°C except for the cases when program rate was zero.

methyl moieties in MOM and MEM groups **3a–f** and **4a–f** were 0.80–22.0 Hz and 0.00–11.6 Hz, respectively, separation of acetal methylene signals were not detected except in the case of **3f**.

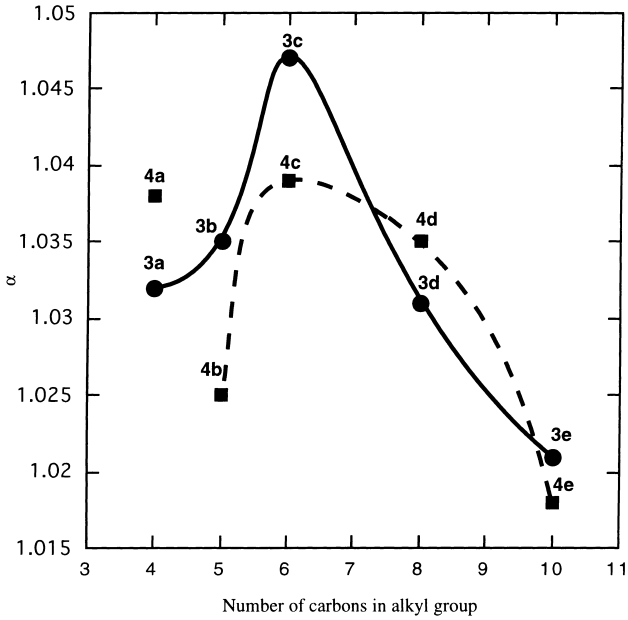


Fig. 2. Plots of separation factor (α) vs. alkyl carbon chain length of **3a–e** and **4a–e**. Normalized GC conditions: column, TC-WAX (0.25 mm i.d.×30 m, GL Science); carrier, 70 ml (He, split ratio, 100:1); initial temperature, 120°C was held for 10 min; program rate, 4°C/min; final temperature, 200°C.

3. Conclusion

As described above, it was found that enantiomerically pure TFLA is a chiral derivatizing agent for chiral secondary alcohols and the protocol with tandem steps including *O*-alkylation provides a high performance way for determination of optical purity of chiral alcohols using GC and ^{19}F-NMR.

4. Experimental

TFLA was prepared by nitric acid oxidation of (*S*)-trifluoropropene oxide, which was supplied by Japan Energy. 1,1,1-Trifluoroalkan-2-ols were supplied by Morita Chemical. ^{1}H-NMR were recorded with JEOL GSX-400 (400 MHz) spectrometer in $CDCl_3$. Chemical shifts were recorded in ppm, downfield from internal tetramethylsilane.

Table 5
^{19}F-NMR shift difference of **3** and **4**[a]

O-MOM form		*O*-MEM form	
Ester **3**	$\Delta\delta$ (Hz)	Ester **4**	$\Delta\delta$ (Hz)
3a	4.52	**4a**	5.08
3b	3.95	**4b**	3.95
3c	2.49	**4c**	4.23
3d	5.08	**4d**	2.26
3e	4.38	**4e**	6.21
3f	2.59	**4f**	1.65
3j	2.03	**4j**	1.88
3s	2.35	**4s**	2.78

[a] Hitachi R-1200F (56.46 MHz) spectrometer was used. Solvent: $CDCl_3$.

^{19}F-NMR spectra were recorded with a Hitachi R-1200F (56.46 MHz) spectrometer in $CDCl_3$ for isolated samples, and chemical shifts were reported in ppm downfield from external CF_3CO_2H. Infrared (IR) spectra were obtained on a JASCO A-120 spectrometer and all spectra were reported in wave numbers (cm^{-1}), with the reference being at the 1601.4 cm^{-1} absorption of a polystyrene film. High resolution mass spectra (HRMS) were taken on a JEOL DX-300 spectrometer operating with EI mode.

4.1. General procedure for TFLA esters **2**

A solution of alcohol **1** (1 mmol) and TFLA (1.2 mmol) in benzene (40 ml) was refluxed using Dean-Stark trap. The completion of the reaction was confirmed by monitoring using ^{19}F-NMR and/or GC. Typically, the reaction completed within 4 h. For ^{19}F-NMR and GC analysis for diastereomeric separation, the reaction mixture could be directly used as the samples. For ^{1}H-NMR and LC analysis to separate diastereomeric signals or peaks, the reaction mixture was treated as follows: Benzene was evaporated under reduced pressure and hexane (40 ml) was added into the residual syrup. After trituration, the hexane layer was separated from unreacted TFLA. The hexane solution was concentrated and dried-up to produce the corresponding ester **2**. If further purification was necessary, distillation or dry column flash chromatography (silica gel, hexane) was adopted.

2-Butyl 3,3,3-trifluoro-2-hydroxypropionate (**2a**): Yield 98%. ^{1}H-NMR δ 0.918 and 0.937 (3H, t, J=7.2, 7.0 Hz), 1.285 and 1.317 (3H, d, J=6.0 Hz), 1.60–1.72 (2H, m), 3.49 (1H, br), 4.433 and 4.444 (1H, q, J=6.4 Hz), 5.06 (1H, tq, J=3.2, 6.4 Hz). ^{19}F-NMR δ 1.640 and 1.670 (d, J=6.4 Hz). IR (KBr) ν 3550, 1750 cm^{-1}. HRMS (EI): Calcd. for $C_7H_{11}O_3F_3$ 200.0660, found 200.0710.

2-Pentyl 3,3,3-trifluoro-2-hydroxypropionate (**2b**): Yield 95%. ^{1}H-NMR δ 1.232 (3H, t, J=6.0 Hz), 1.284 and 1.317 (3H, d, J=6.0 Hz), 1.34–1.73 (4H, m), 4.449 and 4.457 (1H, q, J=6.8 Hz), 5.12 (1H, q, J=6.8 Hz), 6.02 (1H, br). ^{19}F-NMR δ 1.082 and 1.142 (d, J=6.8 Hz). IR (KBr) ν 3620, 1700 cm^{-1}. HRMS (EI): Calcd. for $C_8H_{13}O_3F_3$ 214.0817, found 214.0883.

2-Hexyl 3,3,3-trifluoro-2-hydroxypropionate (**2c**): Yield 95%. ^{1}H-NMR δ 0.894 and 0.909 (3H, t, J=6.8 Hz), 1.285 and 1.318 (3H, d, J=6.4 Hz), 1.57–1.68 (6H, m), 3.49 (1H, s), 4.434 and 4.441 (1H, q, J=6.8 Hz), 5.11 (1H, m). ^{19}F-NMR δ 1.130 and 1.20 (d, J=6.8 Hz). IR (KBr) ν 3530, 1740 cm^{-1}. HRMS (EI): Calcd. for $C_9H_{15}O_3F_3$ 228.0973, found 228.0905.

2-Octyl 3,3,3-trifluoro-2-hydroxypropionate (**2d**): Yield 96%. ^{1}H-NMR δ 0.881 and 0.887 (3H, d, J=6.8 Hz), 1.282 and 1.315 (3H, d, J=6.4 Hz), 1.40–1.70 (10H, m), 3.46 (1H, s), 4.431 and 4.440 (1H, q, J=6.8 Hz), 5.11 (1H, m). ^{19}F-NMR δ 2.140 and 2.170 (d, J=6.8 Hz). IR (KBr) ν 3400, 1720 cm^{-1}. HRMS (EI): Calcd. for $C_{11}H_{19}O_3F_3$ 256.1286, found 256.1342.

2-Decyl 3,3,3-trifluoro-2-hydroxypropionate (**2e**): Yield 99%. ^{1}H-NMR δ 0.880 and 0.883 (3H, t, J=6.2 Hz), 1.281 and 1.314 (3H, d, J=6.0 Hz), 1.38–1.70 (14H, m), 3.46 (1H, s), 4.439 and 4.449 (1H, q, J=6.8 Hz), 5.11 (1H, m). ^{19}F-NMR δ 1.240 and 1.280 (d, J=6.8 Hz). IR (KBr) ν 3530, 1740 cm^{-1}. HRMS (EI): Calcd. for $C_{13}H_{23}O_3F_3$ 284.1599, found 284.1673.

1-Phenylethyl 3,3,3-trifluoro-2-hydroxypropionate (**2f**): Yield 99%. ^{1}H-NMR δ 1.621 and 1.641 (3H, d, J=6.4 Hz), 3.42 (1H, br), 4.458 and 4.512 (1H, q, J=6.8 Hz). 6.029 and 6.051 (1H, q, J=6.8 Hz). ^{19}F-NMR δ 0.592 and 0.770 (d, J=6.8 Hz). IR (KBr) ν 3300, 1720 cm^{-1}. HRMS (EI): Calcd. for $C_{11}H_{11}O_3F_3$ 248.0660, found 248.0735.

Ethyl (3,3,3-trifluoro-2-hydroxypropanoyl)butanonate (**2g**): Yield 95%. ^{1}H-NMR δ 1.249 and 1.267 (3H, t, J=7.2 Hz) 1.371 and 1.407 (1H, d, J=6.0 Hz), 2.55–2.76 (2H, m), 3.40 (1H, br), 4.14 (2H, m), 4.442 and 4.448 (1H, q, J=6.8 Hz), 5.51 (1H, m). ^{19}F-NMR δ 0.432 and 0.497 (d, J=6.8 Hz). IR (KBr) ν 3560, 1760 cm^{-1}. HRMS (EI): Calcd. for $C_9H_{13}O_5F_3$ 258.0715, found 258.0632.

3-But-1-enyl 3,3,3-trifluoro-2-hydroxypropionate (**2h**): Yield 95%. ^{1}H-NMR δ 1.398 and 1.423 (3H, d, J=6.4 Hz), 1.73 (1H, m), 3.40–3.44 (2H, m), 3.40 (1H, br), 4.442 and 4.459 (1H, q, J=6.8 Hz). ^{19}F-NMR δ 0.621 and 0.690 (d, J=6.8 Hz). IR (KBr) ν 3540, 1770 cm^{-1}. HRMS (EI): Calcd. for $C_7H_9O_3F_3$ 198.0504, found 198.0573.

3-Oct-1-enyl 3,3,3-trifluoro-2-hydroxypropionate (**2i**): Although the isolated yield 90% was lower than other esters **2**, the yield estimated from ^{19}F-NMR spectrum of the reaction mixture was quantitative. ^{1}H-NMR δ 0.883 and 0.892 (3H, t, J=6.4 Hz) 1.20–1.80 (8H, m), 3.45 (1H, br), 4.461 and 4.478 (1H, q, J=6.8 Hz), 5.38 (1H, q, J=6.0 Hz), 5.24–5.35 (2H, m), 5.73–5.86 (1H, m). ^{19}F-NMR δ 1.708 and 1.746 (d, J=6.8 Hz). IR (KBr) ν 3315, 1770 cm^{-1}. HRMS (EI): Calcd. for $C_{11}H_{17}O_3F_3$ 254.1130, found 254.1056.

3-Hexyl 3,3,3-trifluoro-2-hydroxypropionate (**2j**): Yield 93%. ^{1}H-NMR δ 0.90 (3H, t, J=6.8 Hz), 0.93 (3H, t, J=7.2 Hz), 1.24–1.70 (6H, m), 4.444 and 4.462 (1H, q, J=6.8 Hz), 5.00–5.07 (1H, m). ^{19}F-NMR δ 0.550 and 0.698 (d, J=6.8 Hz). IR (KBr) ν 3325, 1720 cm^{-1}. HRMS (EI): Calcd. for $C_9H_{15}O_3F_3$ 228.0973, found 228.0900.

1,1,1-Trifluoro-2-butyl 3,3,3-trifluoro-2-hydroxypropionate (**2k**): Yield 98%. ^{1}H-NMR δ 1.027 and 1.032 (3H, t, J=7.6 Hz), 1.80–1.90 (4H, m), 4.44 (1H, q, J=6.8 Hz), 5.35 (1H, m), 5.80 (1H, br). ^{19}F-NMR δ −0.589 and −0.621 (3F, d, J=7.2 Hz), 1.350 and 1.380 (3F, d, J=6.8 Hz). IR (KBr) ν 3345, 1710 cm^{-1}. HRMS (EI): Calcd. for $C_7H_8O_3F_6$ 254.0377, found 254.0302.

1,1,1-Tri-fluoro-2-pentyl 3,3,3-trifluoro-2-hydroxypropionate (**2l**): Yield 95%. ^{1}H-NMR δ 0.963 and 0.967 (3H, t, J=7.6 Hz), 1.80–1.90 (4H, m), 3.62 (1H, q, J=6.8 Hz), 4.62 (1H, m), 4.46 (1H, br). ^{19}F-NMR δ −0.590 and −0.621 (3F, d, J=7.2), 1.320 and 1.353 (3F, d, J=6.8 Hz), IR (KBr) ν 3340, 1760 cm^{-1}. HRMS (EI): Calcd. for $C_8H_{10}O_3F_6$ 268.0534, found 268.0452.

1,1,1-Trifluoro-2-hexyl l 3,3,3-trifluoro-2-hydroxypropionate (**2m**): Yield 93%. ^{1}H-NMR δ 0.950 and 0.955 (3H, t, J=7.6 Hz), 1.37–1.50 (6H, m), 3.32 (1H, br), 4.60 (1H, q, J=6.8 Hz), 5.40 (1H, m). ^{19}F-NMR δ −0.540 and −0.575 (3F, d, J=7.2), 1.250 and 1.293 (3F, d, J=6.8 Hz). IR (KBr) ν 3355, 1760 cm^{-1}. HRMS (EI): Calcd. for $C_9H_{12}O_3F_6$ 282.0691, found 282.0602.

1,1,1-Trifluoro-2-octyl l 3,3,3-trifluoro-2-hydroxypropionate (**2n**): Yield 92%. ^{1}H-NMR δ 0.876 and 0.879 (3H, t, J=7.6 Hz), 1.20–1.31 (10H, m), 3.50 (1H, br), 3.90 (1H, q, J=6.8 Hz), 5.40 (1H, m). ^{19}F-NMR δ −0.486 and −0.522 (3F, d, J=7.2), 1.245 and 1.285 (3F, d, J=6.8 Hz). IR (KBr) ν 3360, 1770 cm^{-1}. HRMS (EI): Calcd. for $C_{11}H_{16}O_3F_6$ 310.1004, found 310.0904.

1,1,1-Trifluoro-2-decyl l 3,3,3-trifluoro-2-hydroxypropionate (**2o**): Yield 98%. ^{1}H-NMR δ 0.885 and 0.888 (3H, t, J=7.6 Hz), 1.27–1.57 (10H, m), 3.32 (1H, br), 3.60 (1H, q, J=6.8 Hz), 5.40 (1H, m). ^{19}F-NMR δ −0.440 and −0.478 (3F, d, J=7.2), 1.255 and 1.287 (3F, d, J=6.8 Hz). IR (KBr) ν 3380, 1740 cm^{-1}. HRMS (EI): Calcd. for $C_{13}H_{20}O_3F_6$ 338.1317, found 338.1202.

3-Octyl 3,3,3-trifluoro-2-hydroxypropionate (**2p**): Yield 92%. ^{1}H-NMR δ 0.878 and 0.915 (3H, t, J=7.2 Hz), 1.28–1.32 (9H, m), 1.56–1.70 (4H, m), 3.475 and 3.479 (1H, d, J=2.6 Hz), 4.446 and 4.464 (1H, q, J=6.8 Hz), 5.11 (1H, m). ^{19}F-NMR δ 0.545 and 0.588 (d, J=6.8 Hz). IR (KBr) ν 3590, 1770 cm^{-1}. HRMS (EI): Calcd. for $C_{11}H_{19}O_3F_3$ 256.1286, found 256.1212.

3-Decyl 3,3,3-trifluoro-2-hydroxypropionate (**2q**): Yield 99%. ^{1}H-NMR δ 0.878 and 0.888 (3H, t, J=6.8 Hz), 0.909 and 0.927 (3H, t, J=6.0 Hz), 1.27–1.66 (16H, m), 3.48 (1H, br), 4.434 and 4.453 (1H, q, J=6.8 Hz), 5.08 and 5.10 (1H, m). ^{19}F-NMR δ 0.567 and 0.589 (d, J=6.8 Hz). IR (KBr) ν 3540, 1710 cm^{-1}. HRMS (EI): Calcd. for $C_{13}H_{23}O_3F_3$ 284.1599, found 284.1696.

2-Methylbutyl 3,3,3-trifluoro-2-hydroxypropionate (**2r**): Yield 97%. ^{1}H-NMR δ 1.249 and 1.267 (3H, t, J=6.8 Hz), 1.371 and 1.407 (3H, d, J=6.0 Hz), 2.55–2.76 (3H, m), 3.40 (1H, br), 4.14 (2H, m), 4.434 and 4.453 (1H, q, J=6.8 Hz), 5.08 (1H, m). ^{19}F-NMR δ 0.432 and 0.479 (d, J=6.8 Hz). IR (KBr) ν 3520, 1710 cm^{-1}. HRMS (EI): Calcd. for $C_8H_{13}O_3F_3$ 214.0817, found 214.0887.

2-(3,3,3-Trifluoro-2-hydroxypropionyl)-3,3-dimethylbultanolide (**2s**): Although the isolated yield 88% was lower than other esters **2**, the yield estimated from ^{19}F-NMR spectrum of the reaction mixture was quantitative. ^{1}H-NMR δ 1.147 and 1.160 (3H, s), 1.232 and 1.258 (3H, s), 3.95 (1H, d, J=8.8 Hz), 4.03 (1H, d, J=8.8 Hz), 4.14 (1H, s), 4.710 and 4.767 (1H, q, J=6.8 Hz), 5.458 and 5.524 (1H, s). ^{19}F-NMR δ 0.767 and 0.795 (d, J=6.8 Hz). IR (KBr) ν 3530, 1750 cm^{-1}. HRMS (EI): Calcd. for $C_9H_{11}O_5F_3$ 256.0559, found 256.0610.

(1S, 2R, 5S)-(+)- and (1R, 2S, 5R)-(−)mentyl (S)-3,3,3-trifluoro-2-hydroxypropionate (**2t**): Yield 91%. ^{1}H-NMR δ 0.727 and 0.780 (3H, d, J=6.8 Hz), 0.82–2.45 (15H, m), 3.42 (1H, s), 3.94 (1H, m), 4.820 and 4.895 (1H, q, J=7.2 Hz). ^{19}F-NMR δ 0.500 and 0.611 (d, J=6.8 Hz). IR (KBr) ν 3520, 1720 cm^{-1}. HRMS (EI): Calcd. for $C_{13}H_{21}O_3F_3$ 282.14428, found 282.1513.

4.2. General procedure for O-alkylated TFLA esters 3 and 4

A solution of ester **2** (0.5 mmol) in THF (5.0 ml) was added into a suspension of sodium hydride (0.5 mmol) in THF (5.0 ml) at 0°C, and then, a solution of MOM or MEM chloride (0.6 mmol) in THF (5.0 ml) was dropped into the mixture at 0°C. After stirring for 2 h at room temperature, the reaction mixture was concentrated in vacuo and the residue was extracted with ether. The ethereal solution was dried over anhydrous sodium sulfate. The syrup obtained by evaporation of the ethereal solution was purified by dry column flash chromatography (silica gel, hexane). Although the isolated yields were not high, the yields determined by ^{19}F-NMR of the reaction mixture using benzotrifluoride as an internal standard were quantitative values almost in every case.

2-Butyl 3,3,3-trifluoro-2-(methoxymethoxy)propionate (**3a**): Yield 69%. ^{1}H-NMR δ 0.915 and 0.925 (3H, t, J=7.6 Hz), 1.266 and 1.281 (3H, d, J=5.6 Hz), 1.58–1.69 (2H, m) 3.436 and 3.439 (3H, s), 4.52 (1H, q, J=6.8 Hz), 4.79 (2H, s), 5.01 (1H, m). ^{19}F-NMR δ 3.000 and 3.080 (d, J=7.6 Hz). HRMS (EI): Calcd. for $C_9H_{15}O_4F_3$ 244.0922, found 244.0835.

2-Pentyl 3,3,3-trifluoro-2-(methoxymethoxy)propionate (**3b**): Yield 93%. ^{1}H-NMR δ 0.915 and 0.925 (3H, t, J=7.6 Hz), 1.265 and 1.281 (3H, d, J=6.0 Hz), 1.30–1.70 (4H, m), 3.434 and 3.436 (3H, s), 4.51 (1H, q, J=6.8 Hz), 4.78 (2H, s), 5.08 (1H, m). ^{19}F-NMR δ 3.308 and 3.378 (d, J=6.8 Hz). HRMS (EI): Calcd. for $C_{10}H_{17}O_4F_3$ 258.1079, found 258.1004.

2-Hexyl 3,3,3-trifluoro-2-(methoxymethoxy)propionate (**3c**): Yield 77%. ^{1}H-NMR δ 0.892 and 0.900 (3H, t, J=6.4 Hz), 1.266 and 1.282 (3H, d, J=6.0 Hz), 1.31–1.72 (6H, m), 3.436 and 3.444 (3H, s), 4.51 (1H, q, J=7.2 Hz), 4.78 (2H, s), 5.06 (1H, m). ^{19}F-NMR δ 3.150 and 3.194 (d, J=7.2 Hz). HRMS (EI): Calcd. for $C_{11}H_{19}O_4F_3$ 272.1235, found 272.1178.

2-Octyl 3,3,3-trifluoro-2-(methoxymethoxy)propionate (**3d**): Yield 88%. ^{1}H-NMR δ 0.892 and 0.900 (3H, t, J=6.8 Hz), 1.266 and 1.282 (3H, d, J=6.0 Hz), 1.29–1.75 (10H, m), 3.436 and 3.438 (3H, s), 4.51 (1H, q, J=6.8 Hz), 4.78 (2H, s), 5.01 (1H, m). ^{19}F-NMR δ 3.225 and 3.315 (d, J=6.8 Hz). HRMS (EI): Calcd. for $C_{13}H_{23}O_4F_3$ 300.1548, found 300.1626.

2-Decyl 3,3,3-trifluoro-2-(methoxymethoxy)propionate (**3e**): Yield 84%. ^{1}H-NMR δ 0.881 and 0.884 (3H, t, J=6.0 Hz), 1.263 and 1.278 (3H, d, J=6.0 Hz), 1.19–1.70 (14H, m), 3.434 and 3.436 (3H, s), 4.51 (1H, q, J=6.8 Hz), 4.78 (2H, s), 5.05 (1H, m). ^{19}F-NMR δ 3.338 and 3.16 (d, J=7.6 Hz). HRMS (EI): Calcd. for $C_{15}H_{27}O_4F_3$ 328.1861, found 328.1806.

1-Phenylethyl 3,3,3-trifluoro-2-(methoxymethoxy)propionate (**3f**): Yield 89%. ^{1}H-NMR δ 1.597 and 1.612 (3H, d, J=6.8 Hz), 3.337 and 3.392 (3H, s), 4.544 and 4.557 (1H, q, J=6.4 Hz), 4.741 and 4.749 (2H, s) 6.01 (1H, q, 6.4 Hz), 7.35 (5H, m). ^{19}F-NMR δ 3.208 and 3.254 (d, J=6.4 Hz). HRMS (EI): Calcd. for $C_{13}H_{15}O_4F_3$ 292.0922, found 292.0861.

3-Hexyl 3,3,3-trifluoro-2-(methoxymethoxy)propionate (**3j**): Yield 81%. ^{1}H-NMR δ 0.906 and 0.914 (3H, t, J=5.8 Hz), 0.922 and 0.932 (3H, t, J=6.0 Hz) 1.18–1.79 (6H, m), 3.390 and 3.393 (3H, s), 4.60 (1H, q, J=6.8 Hz), 4.81 (2H, s), 5.00 (1H, m). ^{19}F-NMR δ 4.120 and 4.126 (d, J=6.8 Hz). HRMS (EI): Calcd. for $C_{11}H_{19}O_4F_3$ 272.1235, found 272.1287.

2-[3,3,3-Trifluoro-2-(methoxymethoxy)propionyloxy]-3,3-dimethylbutanolide (**3s**): Yield 61%. ^{1}H-NMR δ 1.121 and 1.148 (3H, s), 1.216 and 1.243 (3H, s) 3.452 and 3.504 (3H, s), 3.96 (1H, d, J=6.8 Hz) 4.04 (1H, d, J=8.8 Hz), 4.15 (2H, s), 4.56 (1H, q, J=7.2 Hz), 5.012 and 5.029 (1H, m). ^{19}F-NMR δ 3.000 and 3.042 (d, J=7.2 Hz). HRMS (EI): Calcd. for $C_{11}H_{15}O_6F_3$ 300.0821, found 300.0713.

2-Butyl 3,3,3-trifluoro-2-[(2-methoxyethoxy)methoxy]-propionate (**4a**): Yield 70%. ^{1}H-NMR δ 0.909 and 0.923 (3H, t, J=7.6 Hz), 1.258 and 1.277 (3H, d, J=6.4 Hz) 1.59–1.67 (2H, m), 3.38 (3H, s), 3.53–3.56 (2H, m), 3.78–3.80 (2H, m), 4.592 and 4.595 (1H, q, J=6.8 Hz) 4.88 (2H, s), 5.00 (1H, m). ^{19}F-NMR δ 3.270 and 3.360 (d, J=6.8 Hz). HRMS (EI): Calcd. for $C_{11}H_{15}O_5F_3$ 288.1185, found 288.1104.

2-Pentyl 3,3,3-trifluoro-2-[(2-methoxyethoxy)methoxy]-propionate (**4b**): Yield 83%. ^{1}H-NMR δ 0.916 and 0.935 (3H, t, J=6.0 Hz), 1.282 and 1.316 (3H, d, J=6.0 Hz) 1.36–1.73 (4H, m), 3.406 and 3.414 (3H, s), 3.53–3.60 (2H, m), 3.71–3.80 (2H, m), 4.440 and 4.448 (1H, q, J=6.8 Hz) 4.819 and 4.828 (2H, s), 5.11 (1H, m). ^{19}F-NMR δ 2.900 and 2.970 (d, J=6.8 Hz). HRMS (EI): Calcd. for $C_{11}H_{15}O_5F_3$ 302.1341, found 302.1248.

2-Hexyl 3,3,3-trifluoro-2-[(2-methoxyethoxy)methoxy]-propionate (**4c**): Yield 85%. ^{1}H-NMR δ 0.880 and 0.884 (3H, t, J=6.8 Hz), 1.144 and 1.204 (3H, d, J=6.0 Hz) 1.28–1.31 (6H, m), 3.401 and 3.409 (3H, s), 3.56–3.60 (2H, m), 3.71–3.77 (2H, m), 4.429 and 4.42 (1H, q, J=7.2 Hz) 4.749 and 4.758 (2H, s), 4.96 (1H, m). ^{19}F-NMR δ 3.076 and 3.151 (d, J=7.2 Hz). HRMS (EI): Calcd. for $C_{13}H_{23}O_5F_3$ 316.1498, found 316.1402.

2-Octyl 3,3,3-trifluoro-2-[(2-methoxyethoxy)methoxy]-propionate (**4d**): Yield 70%. ^{1}H-NMR δ 0.882 and 0.886 (3H, t, J=6.8 Hz), 1.152 and 1.165 (3H, d, J=6.0 Hz) 1.27–1.32 (10H, m), 3.404 and 3.412 (3H, s), 3.57-3.59 (2H, m), 3.71–3.77 (2H, m), 4.37 and 4.445 (1H, q, J=7.2 Hz) 4.75 (2H, s), 5.10 (1H, m). ^{19}F-NMR δ 3.108 and 3.220 (d, J=7.2 Hz). HRMS (EI): Calcd. for $C_{15}H_{27}O_5F_3$ 344.1811, found 344.1704.

2-Decyl 3,3,3-trifluoro-2-[(2-methoxyethoxy)methoxy]-propionate (**4e**): Yield 70%. ^{1}H-NMR δ 0.879 and 0.882 (3H, t, J=5.8 Hz), 1.254 and 1.274 (3H, d, J=6.4 Hz) 1.28–1.68 (14H, m), 3.382 and 3.384 (3H, s), 3.54 (2H, t, J=4.6 Hz), 3.79 (2H, t, J=4.6 Hz) 4.584 (1H, q, J=6.8 Hz) 4.879 and 4.880 (2H, s), 5.05 (1H, m). ^{19}F-NMR δ 3.558 and 3.668 (d, J=7.2 Hz). HRMS (EI): Calcd. for $C_{17}H_{31}O_5F_3$ 372.2124, found 372.1997.

1-Phenylethyl 3,3,3-trifluoro-2-[(2-methoxyethoxy)-methoxy]propionate (**4f**): Yield 93%. ^{1}H-NMR δ 1.590 and 1.609 (3H, d, J=6.8 Hz), 3.366 and 3.395 (3H, s), 3.47–3.49 (2H, m), 3.56–3.58 (2H, m), 4.614 and 4.633 (1H, q, J=7.2 Hz), 4.843 and 4.848 (2H, s), 6.000 and 6.005 (1H, q, J=6.4 Hz) 7.28–7.38 (5H, br). ^{19}F-NMR δ 3.390 and 3.419 (d, J=7.2 Hz). HRMS (EI): Calcd. for $C_{15}H_{19}O_5F_3$ 336.1185, found 336.1306.

3-Hexyl 3,3,3-trifluoro-2-[(2-methoxyethoxy)methoxy]-propionate (**4j**): Yield 83%. ^{1}H-NMR δ 0.904 and 0.907 (3H, t, J=5.4 Hz), 0.920 and 0.926 (3H, t, J=6.0 Hz) 1.19–1.78 (6H, m), 3.382 and 3.384 (3H, s), 3.52–3.58 (2H, m), 3.77-3.81 (2H, m), 4.610 (1H, q, J=6.8 Hz) 4.88 (2H, s), 4.99 (1H, m). ^{19}F-NMR δ 4.000 and 4.033 (d, J=6.8 Hz). HRMS (EI): Calcd. for $C_{13}H_{23}O_5F_3$ 316.1498, found 316.1406.

2-[3,3,3-Trifluoro-2-[(2-methoxyethoxy)methoxy]propionyloxy]-3,3-dimethylbutanolide (**4s**): Yield 67%. ^{1}H-NMR δ 1.105 and 1.162 (3H, s), 1.209 and 1.259 (3H, s), 3.413 and 3.427 (3H, s), 3.57–3.60 (2H, m), 3.71–3.73 (2H, m), 3.97 (1H, d, J=7.8 Hz), 4.05 (1H, d, J=7.8 Hz), 4.55 (1H, q, J=6.8 Hz), 5.46 and 5.53 (1H, s). ^{19}F-NMR δ 3.666 and 3.715 (d, J=6.8 Hz). HRMS (EI): Calcd. for $C_{13}H_{19}O_7F_3$ 344.1083, found 344.1159.

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