# Chemistry of Novel Compounds with Multifunctional Carbon Structure. VI.[1] Synthetic Studies and $^{19}$F-Nuclear Magnetic Resonance Investigation of Novel α,α-Disubstituted Fluoroacetates

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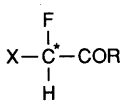
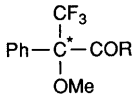
**As a part of our work on synthetic studies of chiral monofluoro compounds and molecular design of efficient reagents for optical purity determination, we focused on novel α,α-disubstituted α-fluoroacetic acids (8a—d) ($R^1$ = Me, Ph; $R^2$ = C≡CPh, Me, Bu). The ethyl esters (13a—d) were prepared by introduction of alkyl groups into the appropriate α-keto acids (9a,b) followed by fluorination of the corresponding hydroxy-esters (12a—d) with diethylaminosulfur trifluoride (DAST). For comparison with Mosher's reagent (2-methoxy-2-trifluoromethylphenylacetic acid, (MTPA)), the ethyl esters (13a—d) were converted into three representative diastereoisomers, (14a—d), (15a—d), and (16a—d), and $^{19}$F-nuclear magnetic resonance ($^{19}$F-NMR) chemical shift differences between pairs of diastereoisomers ($\Delta\delta$) were obtained. These α,α-disubstituted α-fluoroacetate derivatives have much larger $\Delta\delta$ values than the corresponding derivatives of MTPA, which strongly indicates that the acids (8a—d) can potentially be better reagents for ee determination than MTPA. The influence on the $\Delta\delta$ values of the steric effects which arise upon introduction of the two substituents ($R^1$ and $R^2$) on the fluorine-bearing chiral center is also discussed.**

**Keywords** $^{19}$F-NMR; multifunctional carbon compound; 2-methoxy-2-trifluoromethylphenylacetic acid; ee determination; magnetic influence; substituted fluoroacetate; diethylaminosulfur trifluoride

In the course of studies aimed at developing general synthetic methodology for chiral monofluoro compounds and probing the structural requirements of efficient reagents for enantiomeric excess (ee) determination, we reported[2] the synthesis and fluorine nuclear magnetic resonance ($^{19}$F-NMR) investigation of four compounds (**1a—d**) which have heteroatom-centered groups at the α position of various fluoroacetates (Chart 1). Although the diastereoisomers derived from these compounds gave larger $\Delta\delta$ values in general than those given by 2-methoxy-2-trifluoromethylphenylacetic acid (MTPA) (**2**, R = OH),[3] we encountered difficulty in the preparation of the corresponding carboxylic acids (**1a—d**, R = OH) because of high reactivity due to the multifunctional carbon structure.[4]



**1**



**2**

**a**: X = Br **c**: X = OPh

**b**: X = NPhth **d**: X = SPh

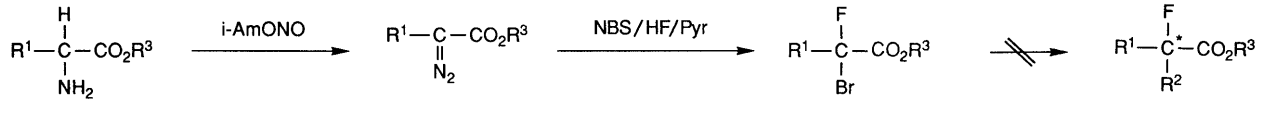
R = OH, OEt, OCH(Me)Et, OCH(Me)Ph, NHCH(Me)Ph

Chart 1

To overcome this problem we decided to investigate synthetic approaches to, as well as the chemical and magnetic properties of, the fairly crowded molecule (**8**), in which two alkyl groups of different bulkiness are introduced at the α position of fluoroacetate. The phenyl group seemed to us to be indispensable as one substituent ($R^1$) of the two, because of its steric and possible electronic effects, as already suggested by our preliminary study.[2] We focused on an alkynyl group, in addition to some relatively small alkyl groups, as the other substituent ($R^2$), because we anticipated the possibility of dehydrofluorination *via* β-elimination of the target compounds. The chemical reactivity of the novel chiral tertiary fluorides adjacent to a carboxyl group was also of interest since no general approach to the synthesis of such fluorides has been published in spite of increasing interest in them in the fields of synthetic[5] and biological[6] chemistry.

## Results and Discussion

**Synthetic Studies**[7] Initial access to the target molecules (**8**) was attempted through the 2-bromo-2-fluorocarboxylic esters (**5a—c**), which were prepared as follows. α-Amino esters (**3a—c**) were treated with isoamyl nitrite to give the diazo-esters (**4a—c**)[8] in yields of 75—90%, and then **4a—c** were reacted with *N*-bromosuccinimide (NBS) in hydrogen fluoride–pyridine.[9] Although **5a, b** were obtained successfully, the yield of **5c** was poor, presumably due to the low




**3** **4** **5**: $R^3$ = Et, $CH_2Ph$ **7**: $R^3$ = Et, $CH_2Ph$

**6**: $R^3$ = H **8**: $R^3$ = H

**a**: $R^1$ = Me, $R^3$ = Et, $CH_2Ph$

**b**: $R^1$ = $CH_2Ph$, $R^3$ = Et, $CH_2Ph$

**c**: $R^1$ = Ph, $R^3$ = Et, $CH_2Ph$

Chart 2

electron density at the benzylic site of **4c**. Attempted introduction of another alkyl group ($R^2$) into the esters (**5a, b**) or the corresponding acids (**6a, b**), either in an electrophilic (Zn then $R^2X$)[10] or a radical ($Bu_3SnR^2$, *etc.*)[11,12] manner, did not give the desired compounds, **7a, b** or **8a, b**, yielding instead unwanted products derived mainly from dehydrobromination or alkylation at the carbonyl moiety (Chart 2).

We anticipated that alkylation of an α-keto acid followed by fluorination could be an alternative route to the target structure. Thus, pyruvic acid (**9a**) or benzoylformic acid (**9b**) was reacted with two molar equivalents of alkyl-lithium (**10**) to give the hydroxy-acids (**11a—d**). These acids (**11a—d**) proved very difficult to purify, so the crude products were converted, without isolation, into the corresponding ethyl esters (**12a—d**) by Fischer's method in yields of 30—71% from **9a, b**. Fluorination of **12a—d** with diethylaminosulfur trifluoride (DAST) proceeded successfully to afford the fluoro-esters (**13a—d**) in yields of 65—100%. The ethyl esters (**13a—d**) or corresponding carboxylic acids (**8a—d**) were then converted to three representative diastereoisomers, *sec*-butyl esters (**14a—d**), α-phenylethyl esters (**15a—d**), and α-phenylethylamides (**16a—d**), by the methods[2] described in our previous paper (Chart 3).

**NMR Study** Little if any useful information could be obtained from $^1$H-NMR data for the derivatives (**14—16**) because the chemical shift differences for each pair of diastereoisomers ($\Delta\delta$) are generally very small. Furthermore, the signals of most protons are overlapped by those of other protons in the same molecule (see Experimental).

In contrast to the $^1$H-NMR data, the corresponding $^{19}$F-NMR $\Delta\delta$ values are noteworthy (Table I). Since many of the derivatives prepared have much larger $\Delta\delta$ values than those derived from MTPA, the structural effect of the fluorine atom directly attached to the chiral center is obvious.[2] It should also be noted that the existence of three different sizes of substituents, $R_L$ (Ph), $R_M$ (C≡CPh, Me, or Bu), and $R_S$ (F), appears to be essential in obtaining these larger $\Delta\delta$ values. The relatively small $\Delta\delta$ values in general for **14a—16a** could be attributable to the similar degrees of bulkiness of the two substituents, *i.e.*, the Me group and the linear shape of C≡CPh group. The fluorine nuclei of these compounds show much sharper signals ($w_{1/2}$ 5—7 Hz) as compared with MTPA ($w_{1/2}$ 12—15 Hz), where both the F and OMe signals are broad due to the long-range coupling between the two nuclei.[3] However, the fluorine signals of **14c, d—16c, d** are split as a result of coupling with the α-protons of the methyl or butyl group, although the

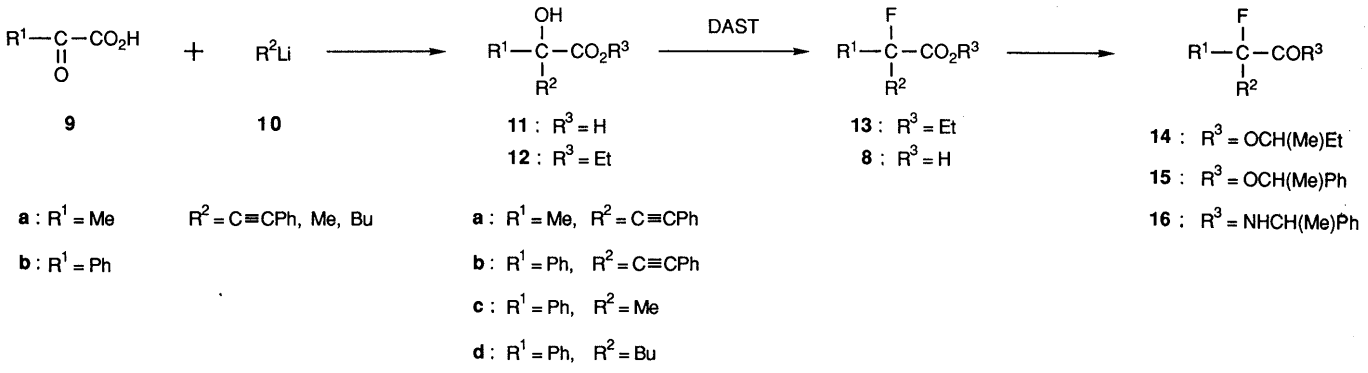



Chart 3

TABLE I. Values of $^{19}$F Chemical Shift Difference $\Delta\delta$ (in Hz) of Diastereoisomers (**14—16**) by 254 MHz $^{19}$F-NMR[a]

| | $R^1/R^2$ | | | | |
|---|---|---|---|---|---|
| | Me/C≡CPh (**a**) | Ph/C≡CPh (**b**) | Ph/Me (**c**) | Ph/Bu (**d**) | (MTPA) |
| $R^3$ = –O–C(Et)(Me)–H (**14**) | 22.0 | 80.9 | 180.2 | 150.8 | n.d. |
| $R^3$ = –O–C(Ph)(Me)–H (**15**) | 71.7 | 93.8 | 150.7 | 53.3 | 51.5 |
| $R^3$ = –NH–C(Ph)(Me)–H (**16**) | 3.7 | 189.4 | 165.5 | 152.6 | 45.9 |

a) See Experimental for details of conditions and method for determination of $\Delta\delta$ values. n.d.: not detectable.

coupling constants ($J=20$—$27$ Hz) are much smaller than the $\Delta\delta$ values. Taking account of these facts, it appears that compound **8b** ($R^1=Ph$, $R^2=C\equiv CPh$) is the best candidate to surpass the capability of MTPA.

**Synthetic Studies on Optically Active Reagents** Another difficulty with MTPA lies in the annoying fact that the optical purity of commercially available MTPA is not reliable from lot to lot. This apparently derives from the fact that the optically active MTPA is prepared by repeated recrystallization of a diastereoisomeric mixture of racemic MTPA as its salt with (+)- or (−)-α-phenethylamine. An alternative and promising means for preparing the optically pure acids (**8a—d** in Chart 3) is the diastereoisomeric separation of the corresponding optically active α-phenylethyl esters followed by saponification. However, the phenylethyl esters were strongly resistant to the usual saponificative[13] and non-saponificative[14] hydrolyses, presumably due to the steric crowding of both the acid and the alcohol moieties of the ester structure. After considerable investigation, we discovered that this step proceeds smoothly under very mild conditions of hydrogenation using palladium hydroxide catalyst.[15] Thus, the more polar diastereoisomer[16] of α-fluoro-*N*-phthalylglycine (*R*)-α-phenylethyl ester (**1b**, R=OCH(Me)Ph) was submitted to hydrogenolysis using 20% palladium hydroxide on charcoal at atmospheric pressure to produce the optically active acid, (+)-**1b** (R=OH), in almost quantitative yield.[17]

We have thus developed the first convenient route to the novel tertiary fluorides with an adjacent carboxyl group and elucidated the principal steric requirement for obtaining larger $\Delta\delta$ values of the diastereoisomer derivatives. We are now proceeding with further structural design investigations and the preparation of optically active acids *via* the methods mentioned above, in order to discover more practical and efficient reagents which will supplant MTPA.

## Experimental

Infrared (IR) spectra were recorded on a JASCO A-102 spectrometer. $^1$H-NMR spectra were measured in $CDCl_3$ with $Me_4Si$ as an internal standard and recorded on JEOL PMX-60 (60 MHz) and JEOL GX-270 (270 MHz) spectrometers. $^{19}$F-NMR spectra were measured in $CDCl_3$ with $CFCl_3$ as an internal standard and taken with a JEOL GX-270 (254 MHz) spectrometer. Upfield shifts are quoted as negative. Electron impact mass spectra (EI-MS) were taken with a JEOL JMS-D300 spectrometer. Column chromatography and preparative thin layer chromatography (PLC) were performed using Kieselgel 60 (Merck, Art. 9385 and Art. 7748, respectively).

**General Procedure for Preparation of the 2-Bromo-2-fluoro Esters (5a, b)** A solution of a 2-diazo ester (**4**)[8] (5.0 mmol) in $Et_2O$ (10 ml) was added dropwise to a stirred mixture of *N*-bromosuccinimide (2.0 mmol) and 70% hydrogen fluoride–pyridine (5 ml) in $Et_2O$ (10 ml) at 0 °C over a period of 10 min, and the whole mixture was stirred for 30 min. Water (30 ml) was added. The aqueous layer was separated and extracted with $Et_2O$ (20 ml × 3), and the combined ethereal solution was washed with water, saturated $NaHCO_3$, and water, and dried over $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by silica gel (AcOEt–hexane) and/or Sephadex LH-20 (acetone) column chromatography to give the corresponding bromofluoro ester (**5a, b**) in 35—60% yield.

**Ethyl 2-Bromo-2-fluoropropionate (5a, $R^3=Et$)** Colorless oil in 60% yield. IR $\nu_{max}$ (neat) cm$^{-1}$: 1760 (CO). $^1$H-NMR $\delta$: 1.37 (3H, t, $J=7$ Hz, $CH_2\underline{Me}$), 2.28 (2H, d, $J_{H,F}=20$ Hz, CFMe), 4.33 (2H, q, $J=7$ Hz, $CH_2$). High MS: Calcd for $C_5H_8BrFO_2$ (Mol. weight 197.9692), Found: 197.9665 ($M^+$). Calcd for $C_5H_8Br^*FO_2$ (Mol. weight 199.9672), Found: 199.9658 ($M^+$).

**Benzyl 2-Bromo-2-fluoropropionate (5a, $R^3=CH_2Ph$)** Colorless oil in 35% yield. IR $\nu_{max}$ (neat) cm$^{-1}$: 1755 (CO). $^1$H-NMR $\delta$: 2.28 (3H, d, $J_{H,F}=20$ Hz, Me), 5.30 (2H, s, $CH_2$), and 7.42 (5H, s, Ph). High MS: Calcd for $C_{10}H_{10}BrFO_2$ (Mol. weight 259.9848), Found: 259.9756 ($M^+$), Calcd for $C_{10}H_{10}Br^*FO_2$ (Mol. weight 261.9830), Found: 261.9861 ($M^+$).

**Ethyl 2-Bromo-2-fluoro-3-phenylpropionate (5b, $R^3=Et$)** Colorless oil in 56% yield. bp 70—72 °C (0.8 mmHg). IR $\nu_{max}$ (neat) cm$^{-1}$: 1765 (CO). $^1$H-NMR $\delta$: 1.29 (3H, t, $J=7$ Hz, Me), 3.78 (2H, d, $J_{H,F}=21$ Hz, $C\underline{H}_2Ph$), 4.27 (2H, q, $J=7$ Hz, $OCH_2$), 7.37 (5H, s, Ph). MS *m/z*: 275, 277 ($M^++1$), 255, 257 ($M^+-F$), 195 ($M^+-Br$). *Anal.* Calcd for $C_{11}H_{12}BrFO_2$: C, 48.02; H, 4.40. Found: C, 47.91; H, 4.42.

**Benzyl 2-Bromo-2-fluoro-3-phenylpropionate (5b, $R^3=CH_2Ph$)** Colorless oil in 43% yield. IR $\nu_{max}$ (neat) cm$^{-1}$: 1750 (CO). $^1$H-NMR $\delta$: 3.73 (2H, d, $J=23$ Hz, $CFCH_2$), 5.20 (2H, s, $OCH_2$), 7.25 (5H, s, $CFCH_2\underline{Ph}$), 7.35 (5H, s, $OCH_2\underline{Ph}$). High MS: Calcd for $C_{16}H_{14}BrFO_2$ (Mol. weight 336.0161), Found: 336.0112 ($M^+$). Calcd for $C_{16}H_{14}Br^*FO_2$ (Mol. weight 338.0141), Found: 338.0112 ($M^+$).

**General Procedure for Preparation of the Hydroxy-Esters (12a—d)** A solution of alkyl-lithium (RLi, **10**) (10 mmol) in $Et_2O$ or tetrahydrofuran (THF) (10 ml) was added dropwise to a solution of pyruvic acid (**9a**) or benzoylformic acid (**9b**) (5 mmol) in THF (10 ml) over a period of 10 min under an argon atmosphere at −50 °C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 2 h. Evaporation of the solvent gave a brown semisolid, which was dissolved in water (30 ml), and the solution was washed twice with a small amount of $Et_2O$. The aqueous layer was acidified with 1 N hydrochloric acid, then extracted with AcOEt (30 ml × 3), and the combined extract was dried over $MgSO_4$. Evaporation of the solvent gave the corresponding crude hydroxy-acid (**11a—d**) as a yellow oil in 73—92% yield.

A mixture of a crude acid (**11a—d**) in EtOH (10 ml) and one drop of concentrated $H_2SO_4$ was heated at reflux for 2 h. The solvent was evaporated off and the residue was dissolved in $Et_2O$ (50 ml). The ethereal solution was washed with water, saturated $NaHCO_3$, and saturated NaCl, then dried over $MgSO_4$. Evaporation of the solvent gave an oil, which was chromatographed on silica gel to give the corresponding hydroxy-ester (**12a—d**) in 30—71% yield from the acid (**9a, b**).

**Ethyl 2-Hydroxy-2-methyl-4-phenyl-3-butynoate (12a)** Colorless oil in 31% yield. IR $\nu_{max}$ (neat) cm$^{-1}$: 3450 (OH), 2220 (C≡C), 1735 (CO), 1595 (Ph). $^1$H-NMR $\delta$: 1.35 (3H, t, $J=7$ Hz, $CH_2\underline{Me}$), 1.80 (3H, s, C(OH)$\underline{Me}$), 3.71 (1H, br s, OH), 4.35 (2H, q, $J=7$ Hz, $CH_2$), 7.2—7.5 (5H, m, Ph). High MS: Calcd for $C_{13}H_{14}O_3$ (Mol. weight 218.0942), Found: 218.0919 ($M^+$). Calcd for $C_{10}H_9O$ (Mol. weight 145.0653), Found: 145.0642 ($M^+-CO_2Et$).

**Ethyl 2-Hydroxy-2,4-diphenyl-3-butynoate (12b)** Colorless oil in 58% yield. IR $\nu_{max}$ (neat) cm$^{-1}$: 3480 (OH), 2225 (C≡C), 1730 (CO), 1595 (Ph). $^1$H-NMR $\delta$: 1.20 (3H, t, $J=7$ Hz, Me), 4.29 (2H, q, $J=7$ Hz, $CH_2$), 4.4 (1H, br s, OH), 7.2—7.9 (10H, m, Ph × 2). High MS: Calcd for $C_{18}H_{16}O_3$ (Mol. weight 280.1098), Found: 280.1061 ($M^+$). Calcd for $C_{15}H_{11}O$ (Mol. weight 207.0809), Found: 207.0795 ($M^+-CO_2Et$).

**Ethyl 2-Hydroxy-2-phenylpropionate (12c)** Colorless oil in 71% yield. IR $\nu_{max}$ (neat) cm$^{-1}$: 3520 (OH), 1750 (CO), 1600 (Ph). $^1$H-NMR $\delta$: 1.31 (3H, t, $J=7$ Hz, $CH_2\underline{Me}$), 1.79 (3H, s, C(OH)$\underline{Me}$), 3.95 (1H, br s, OH), 4.20 (2H, q, $J=7$ Hz, $CH_2$), 7.2—7.7 (5H, m, Ph). High MS: Calcd for $C_{11}H_{14}O_3$ (Mol. weight 194.0942), Found: 194.0953 ($M^+$). Calcd for $C_8H_9O$ (Mol. weight 121.0653), Found: 121.0656 ($M^+-CO_2Et$).

**Ethyl 2-Hydroxy-2-phenylhexanoate (12d)** Colorless oil in 30% yield. IR $\nu_{max}$ (neat) cm$^{-1}$: 3520 (OH), 1730 (CO), 1595 (Ph). $^1$H-NMR $\delta$: 0.91 (3H, m, $CH_2CH_2\underline{Me}$), 1.1—1.6 (7H, m, $CH_2CH_2$ and $OCH_2\underline{Me}$), 1.9—2.1 (2H, m, C(OH)$C\underline{H}_2$), 7.2—7.8 (5H, m, Ph). High MS: Calcd for $C_{14}H_{20}O_3$ (Mol. weight 236.1411), Found: 236.1384 ($M^+$). Calcd for $C_{12}H_{15}O_2$ (Mol. weight 191.1071), Found: 191.1411 ($M^+-OEt$).

**General Procedure for Preparation of the α-Fluoro-Esters (13a—d) by Reaction of the α-Hydroxy-Esters (12a—d) with DAST** A solution of DAST (3.0 mmol) in $CH_2Cl_2$ (2 ml) was placed in a plastic flask and chilled at −80 °C. To this solution, a solution of a hydroxy-ester (**12a—d**) (1.5 mmol) in $CH_2Cl_2$ (2 ml) was added dropwise with stirring over a period of 10 min under an argon atmosphere. The whole mixture was allowed to warm to room temperature, stirred at room temperature for 2 h, poured into water (30 ml), and extracted with $CH_2Cl_2$ (10 ml × 3). The combined extract was washed with saturated NaCl and dried over $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by silica gel chromatography to give the corresponding fluoro-ester (**13a—d**) in 65—100% yield.

**Ethyl 2-Fluoro-2-methyl-4-phenyl-3-butynoate (13a)** Pale yellow oil in 69% yield. IR $\nu_{max}$ (neat) cm$^{-1}$: 2220 (C≡C), 1750 (CO), 1595 (Ph). $^1$H-NMR $\delta$: 1.35 (3H, t, $J=7.1$ Hz, $CH_2\underline{Me}$), 1.85 (3H, d, $J_{H,F}=20.3$ Hz,

CFMe), 4.33 (2H, q, $J$=7.1 Hz, $CH_2$), 7.3—7.5 (5H, m, Ph). $^{19}$F-NMR $\delta$: −139.87 (q, $J$=20.2 Hz). High MS: Calcd for $C_{13}H_{13}FO_2$ (Mol. weight 220.0899), Found: 220.0894 ($M^+$). Calcd for $C_{10}H_8F$ (Mol. weight 147.0610), Found: 147.0618 ($M^+ - CO_2Et$).

**Ethyl 2-Fluoro-2,4-diphenyl-3-butynoate (13b)** Pale yellow oil in 78% yield. IR $\nu_{max}$ (neat) cm$^{-1}$: 2230 (C≡C), 1760 (CO), 1600 (Ph). $^1$H-NMR $\delta$: 1.20 (3H, t, $J$=7 Hz, Me), 4.30 (2H, q, $J$=7 Hz, $CH_2$), 7.1—7.8 (10H, m, Ph×2). High MS: Calcd for $C_{18}H_{15}FO_2$ (Mol. weight 282.1055), Found: 282.1038 ($M^+$). Calcd for $C_{15}H_{10}F$ (Mol. weight 209.0766), Found: 209.0622 ($M^+ - CO_2Et$).

**Ethyl 2-Fluoro-2-phenylpropionate (13c)** Pale yellow oil in quantitative yield. IR $\nu_{max}$ (neat) cm$^{-1}$: 1750 (CO), 1600 (Ph). $^1$H-NMR $\delta$: 1.26 (3H, t, $J$=7.1 Hz, $CH_2$Me), 1.93 (3H, d, $J_{H,F}$=22.1 Hz, CFMe), 4.22 (2H, q, $J$=7.1 Hz, $CH_2$), 7.3—7.7 (5H, m, Ph). $^{19}$F-NMR $\delta$: −152.06 (d, $J$=22.1 Hz). High MS: Calcd for $C_{11}H_{13}FO_2$ (Mol. weight 196.0899), Found: 196.0876 ($M^+$). Calcd for $C_8H_8F$ (Mol. weight 123.0610), Found: 123.0608 ($M^+ - CO_2Et$).

**Ethyl 2-Fluoro-2-phenylhexanoate (13d)** Pale yellow oil in 65% yield. IR $\nu_{max}$ (neat) cm$^{-1}$: 1740 (CO), 1600 (Ph). $^1$H-NMR $\delta$: 0.89 (3H, m, $CH_2CH_2$Me), 1.2—1.4 (4H, m, $CH_2CH_2$Me), 1.25 (3H, t, $J$=7.1 Hz, $OCH_2$Me), 2.0—2.5 (2H, m, $FCCH_2$), 4.21 (2H, q, $J$=7.1 Hz, $OCH_2$), 7.3—7.6 (5H, m, Ph). $^{19}$F-NMR $\delta$: −165.54 (dd, $J$=27.5, 21.4 Hz). High MS: Calcd for $C_{14}H_{19}FO_2$ (Mol. weight 238.1368), Found: 238.1368 ($M^+$).

Three kinds of diastereoisomers (**14**—**16**) were prepared according to the procedures described in our preceding paper.[2] These compounds were prepared only for obtaining the $\Delta\delta$ values, so the diastereoisomeric mixture was not separated. All spectral data were recorded at 1 : 1 diastereoisomeric ratio and the yields (40—90%) were not optimized.

***sec*-Butyl 2-Fluoro-2-methyl-4-phenyl-3-butynoate (14a)** Colorless oil. IR $\nu_{max}$ (neat) cm$^{-1}$: 2220 (C≡C), 1730 (CO), 1600 (Ph). $^1$H-NMR $\delta$: 0.96 (3H, t, $J$=7.4 Hz, $CH_2$Me), 1.22 and 1.68 ($\Delta\delta$=23.2 Hz), (3H, d, $J$=6.8 Hz, CHMe), 1.68 (2H, m, $CH_2$), 1.92 (3H, d, $J_{H,F}$=20.2 Hz, CFMe), 5.01 (1H, m, CH), 7.25—7.50 (5H, m, Ph). $^{19}$F-NMR $\delta$: −140.10 and −140.02 ($\Delta\delta$=22.0 Hz) (s). High MS: Calcd for $C_{15}H_{17}FO_2$ (Mol. weight 248.1211), Found: 248.1185 ($M^+$). Calcd for $C_{10}H_8F$ (Mol. weight 147.0611), Found: 147.0623 ($M^+ - CO_2Bu^{sec}$).

***sec*-Butyl 2-Fluoro-2,4-diphenyl-3-butynoate (14b)** Colorless oil. IR $\nu_{max}$ (neat) cm$^{-1}$: 2230 (C≡C), 1760 (CO), 1600 (Ph). $^1$H-NMR $\delta$: 0.69 and 0.92 ($\Delta\delta$=62.8 Hz) (3H, t, $J$=7.5 Hz, $CH_2$Me), 1.14 and 1.27 ($\Delta\delta$=35.9 Hz) (3H, d, $J$=6.4 Hz, CHMe), 1.55 (2H, m, $CH_2$Me), 4.96 (1H, m, CH), 7.3—7.8 (10H, m, Ph×2). $^{19}$F-NMR $\delta$: −135.06 and −134.74 ($\Delta\delta$=80.9 Hz) (s). High MS: Calcd for $C_{20}H_{19}FO_2$ (Mol. weight 310.1368), Found: 310.1367 ($M^+$). Calcd for $C_{16}H_{10}FO$ (Mol. weight 237.0715), Found: 237.0709 ($M^+ - OBu^{sec}$).

***sec*-Butyl 2-Fluoro-2-phenylpropionate (14c)** Colorless oil. IR $\nu_{max}$ (neat) cm$^{-1}$: 1740 (CO), 1600 (Ph). $^1$H-NMR $\delta$: 0.77 and 0.81 ($\Delta\delta$=11.2 Hz) (3H, t, $J$=7.5 Hz, $CH_2$Me), 1.17 and 1.20 ($\Delta\delta$=4.9 Hz) (3H, d, $J$=6.4 Hz, CHMe), 1.55 (2H, m, $CH_2$), 1.93 (3H, d, $J_{H,F}$=22.1 Hz, CFMe), 4.89 (1H, m, CH), 7.3—7.6 (5H, m, Ph). $^{19}$F-NMR $\delta$: −151.80 and −151.09 ($\Delta\delta$=180.2 Hz) (d, $J$=22.1 Hz). High MS: Calcd for $C_{13}H_{17}FO_2$ (Mol. weight 224.1212), Found: 224.1166 ($M^+$). Calcd for $C_8H_8F$ (Mol. weight 123.0610), Found: 123.0626 ($M^+ - CO_2Bu^{sec}$).

***sec*-Butyl 2-Fluoro-2-phenylhexanoate (14d)** Colorless oil. IR $\nu_{max}$ (neat) cm$^{-1}$: 1750 (CO). $^1$H-NMR $\delta$: 0.90 (6H, m, $CH_2$Me×2), 1.2—1.4 (7H, m, $CH_2CH_2CH_2$Me and CHMe), 1.55 (2H, m, $CHCH_2$Me), 2.0—2.5 (2H, m, $CH_2CH_2CH_2$Me), 4.9 (1H, m, CH), 7.3—7.6 (5H, m, Ph). $^{19}$F-NMR $\delta$: −165.10 and −164.51 ($\Delta\delta$=150.8 Hz) (dd, $J$=27.6, 20.2 Hz). High MS: Calcd for $C_{16}H_{23}FO_2$ (Mol. weight 266.1681), Found: 266.1722 ($M^+$). Calcd for $C_{11}H_{14}F$ (Mol. weight 165.1079), Found: 165.1079 ($M^+ - CO_2Bu^{sec}$).

**α-Phenylethyl 2-Fluoro-2-methyl-4-phenyl-3-butynoate (15a)** Pale yellow oil. IR $\nu_{max}$ (neat) cm$^{-1}$: 2230 (C≡C), 1760 (CO), 1595 (Ph). $^1$H-NMR $\delta$: 1.63 and 1.64 ($\Delta\delta$=1.1 Hz) (3H, d, $J$=6.6 Hz, CHMe), 1.90 and 1.94 ($\Delta\delta$=9.5 Hz) (3H, d, $J_{H,F}$=20.3 Hz, CFMe), 6.01 and 6.02 ($\Delta\delta$=4.2 Hz) (1H, d, $J$=6.6 Hz, CH), 7.3—7.5 (10H, m, Ph×2). $^{19}$F-NMR $\delta$: −140.42 and −140.13 ($\Delta\delta$=71.7 Hz) (q, $J$=20.3 Hz). High MS: Calcd for $C_{19}H_{17}FO_2$ (Mol. weight 296.1212), Found: 296.1170 ($M^+$). Calcd for $C_8H_9O$ (Mol. weight 121.0654), Found: 121.0684 (OCH(Me)Ph).

**α-Phenylethyl 2-Fluoro-2,4-diphenyl-3-butynoate (15b)** Pale yellow oil. IR $\nu_{max}$ (neat) cm$^{-1}$: 2230 (C≡C), 1760 (CO), 1600 (Ph). $^1$H-NMR $\delta$: 1.46 and 1.57 ($\Delta\delta$=30.3 Hz) (3H, d, $J$=6.6 Hz, Me), 5.97 (1H, m, CH), 7.1—7.8 (15H, m, Ph×3). $^{19}$F-NMR $\delta$: −135.34 and −134.97 ($\Delta\delta$=93.8 Hz) (s). High MS: Calcd for $C_{15}H_{10}F$ (Mol. weight 209.0766), Found: 209.0816 ($M^+ - CO_2CH(Me)Ph$). Calcd for $C_8H_9$ (Mol. weight 105.0704), Found: 105.0669 (CH(Me)Ph).

**α-Phenylethyl 2-Fluoro-2-phenylpropionate (15c)** Pale yellow oil. IR $\nu_{max}$ (neat) cm$^{-1}$: 1750 (CO), 1600 (Ph). $^1$H-NMR $\delta$: 1.50 and 1.52 ($\Delta\delta$=4.6 Hz) (3H, d, $J$=6.6 Hz, CHMe), 1.92 and 1.93 ($\Delta\delta$=3.7 Hz) (3H, d, $J_{H,F}$=3.7 Hz, CHMe), 5.90 (1H, q, $J$=6.8 Hz, CH), 7.2—7.6 (10H, m, Ph×2). $^{19}$F-NMR $\delta$: −151.96 and −151.36 ($\Delta\delta$=150.7 Hz) (q, $J$=22.1 Hz). High MS: Calcd for $C_{17}H_{16}O_2$ (Mol. weight 252.1149), Found: 252.1244 ($M^+ - HF$). Calcd for $C_8H_8F$ (Mol. weight 123.0610), Found: 123.0787 ($M^+ - CO_2CH(Me)Ph$).

**α-Phenylethyl 2-Fluoro-2-phenylhexanoate (15d)** Pale yellow oil. IR $\nu_{max}$ (neat) cm$^{-1}$: 1760 (CO), 1600 (Ph). $^1$H-NMR $\delta$: 0.9 (3H, m, $CH_2$Me), 1.2—1.4 (4H, m, $CH_2CH_2$Me), 1.4—1.6 (3H, m, CHMe), 2.0—2.5 (2H, m, $CFCH_2$), 5.95 (1H, m q, $J$=6.6 Hz, CH), 7.2—7.7 (10H, m, Ph×2). $^{19}$F-NMR $\delta$: −165.08 and −164.88 ($\Delta\delta$=53.3 Hz) (dd, $J$=29.4, 20.3 Hz). High MS: Calcd for $C_{20}H_{23}FO_2$ (Mol. weight 314.1681), Found: 314.1940 ($M^+$). Calcd for $C_{11}H_{14}F$ (Mol. weight 165.1079), Found: 165.1064 ($M^+ - CO_2CH(Me)Ph$).

**2-Fluoro-2-methyl-*N*-(α-phenylethyl)-4-phenyl-3-butynamide (16a)** Colorless crystals. IR $\nu_{max}$ (KBr) cm$^{-1}$: 3360 (NH), 1665 (CO), 1600 (Ph). $^1$H-NMR $\delta$: 1.57 (3H, d, $J$=6.8 Hz, CHMe), 1.90 and 1.94 ($\Delta\delta$=0.5 Hz) (3H, d, $J_{H,F}$=20.2 Hz, CFMe), 5.15 (1H, m, CH), 6.69 (1H, br s, NH), 7.3—7.5 (10H, m, Ph×2). $^{19}$F-NMR $\delta$: −138.22 and −138.20 ($\Delta\delta$=3.7 Hz) (q, $J$=20.2 Hz). High MS: Calcd for $C_{19}H_{18}FNO$ (Mol. weight 295.1533), Found: 295.1324 ($M^+$). Calcd for $C_{10}H_8F$ (Mol. weight 147.0610), Found: 147.0573 ($M^+ - CONHCH(Me)Ph$).

**2-Fluoro-*N*-(α-phenylethyl)-2,4-diphenyl-3-butynamide (16b)** Pale yellow crystals. IR $\nu_{max}$ (KBr) cm$^{-1}$: 3340 (NH), 2230 (C≡C), 1660 (CO), 1600 (Ph). $^1$H-NMR $\delta$: 1.55 and 1.60 ($\Delta\delta$=11.7 Hz) (3H, d, $J$=6.8 Hz, Me), 5.17 (1H, m, CH), 6.87 (1H, br s, NH), 7.2—7.8 (15H, m, Ph×3). $^{19}$F-NMR $\delta$: −131.86 and −131.11 ($\Delta\delta$=189.4 Hz) (s). High MS: Calcd for $C_{24}H_{20}FNO$ (Mol. weight 357.1528), Found: 357.1523 ($M^+$).

**2-Fluoro-*N*-(α-phenylethyl)-2-phenylpropionamide (16c)** Pale yellow crystals. IR $\nu_{max}$ (KBr) cm$^{-1}$: 3370 (NH), 1655 (CO), 1600 (Ph). $^1$H-NMR $\delta$: 1.44 and 1.54 ($\Delta\delta$=26.6 Hz), (2H, d, $J$=6.8 Hz, CHMe), 1.87 and 1.92 ($\Delta\delta$=15.8 Hz) (3H, d, $J$=23.9 Hz, CFMe), 5.08 (1H, q, $J$=6.8 Hz, CH), 6.72 (1H, br s, NH), 7.1—7.6 (10H, m, Ph×2). $^{19}$F-NMR $\delta$: −150.99 and −150.34 ($\Delta\delta$=165.5 Hz) (qd, $J$=23.9, 5.5 Hz). High MS: Calcd for $C_{17}H_{18}FNO$ (Mol. weight 271.1371), Found: 271.1360 ($M^+$). Calcd for $C_8H_8F$ (Mol. weight 123.0610), Found: 123.0602 ($M^+ - CONHCH(Me)Ph$).

**2-Fluoro-*N*-(α-phenylethyl)-2-phenylhexanamide (16d)** Colorless crystals. IR $\nu_{max}$ (KBr) cm$^{-1}$: 3360 (NH), 1685 (CO), 1600 (Ph). $^1$H-NMR $\delta$: 0.91 (3H, m, $CH_2$Me), 1.2—1.4 (4H, m, $CH_2CH_2$Me), 1.4—1.6 (3H, m, CHMe), 2.0—2.5 (2H, m, $CFCH_2$), 5.15 (1H, m, CH), 7.2—7.6 (10H, m, Ph×2). $^{19}$F-NMR $\delta$: −164.43 and −163.85 ($\Delta\delta$=152.6 Hz) (dd, $J$=29.4, 20.2 Hz). High MS: Calcd for $C_{20}H_{24}FNO$ (Mol. weight 313.1841), Found: 313.1875 ($M^+$). Calcd for $C_{11}H_{14}F$ (Mol. weight 165.1079), Found: 165.1071 ($M^+ - CONHCH(Me)Ph$).

**(*R*)-(+)-α-Fluoro-*N*-phthalylglycine (1b, R=OH)** A solution of (*R*)-α-phenylethyl (*R*)-fluoro(phthalimido)acetate (**1b**, R=OCH(Me)Ph) (121 mg, 0.37 mmol) in EtOH (5 ml) was hydrogenolyzed over a catalytic amount of 20% $Pd(OH)_2$ on charcoal at atmospheric pressure for 15 h. When the reaction was complete, the catalyst was removed by filtration and the filtrate was concentrated to give the title compound (81 mg, 98%) as a colorless solid. Recrystallization from AcOEt gave an analytical sample as colorless needles. mp 133—134 °C. $[\alpha]_D^{27}$ +37.7° ($c$=2.0 in EtOH). IR $\nu_{max}$ (KBr) cm$^{-1}$: 3550 (OH), 1780 and 1730 (CO), 1600 (Ar). $^1$H-NMR $\delta$: 6.44 (1H, d, $J_{H,F}$=49 Hz, CFH), 7.9—8.0 (4H, m, Phth). $^{19}$F-NMR $\delta$: −156.02 (d, $J_{F,H}$=49 Hz). MS $m/z$: 223 ($M^+$), 204 ($M^+ - F$), 178 ($M^+ - COOH$). *Anal.* Calcd for $C_{10}H_6NFO_4 \cdot H_2O$: C, 49.80; H, 3.34; N, 5.81. Found: C, 49.75; H, 3.26; N, 6.12.

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