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Chemistry of Novel Compounds Possessing Multifunctional Carbon Atoms. X.[1]) Synthetic Studies of Efficient and Practical Chiral Derivatizing Agents Based on the α-Cyano-α-fluorophenylacetic Acid Structure

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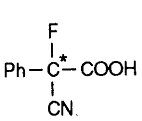
In order to develop efficient chiral derivatizing agents (CDAs) which can be obtained readily in optically active form, synthetic studies of α-cyano-α-fluorophenylacetic acid (CFPA) analogs, 3a—e and CFNA (14a), were made. Carboxylation of 6a—e obtained from 4a—e gave 3a—e in low yield. Alternatively, benzyl cyanides 5b—e were converted successfully to the esters 7b—e, 8b—e, and 9b—e, which were fluorinated with $FClO_3$ to produce the fluoro esters 10b—e, 11b—e, and 12b—d, in good yields. However, the attempted ester cleavage of these compounds did not give 3b—e. Carboxyl group introduction into 5e afforded 13, and fluorination with either F_2 or $FClO_3$ gave complex mixtures.

Carboxylation of the naphthyl analog 16 obtained from 15 did not give 14a. However, fluorination of 18 derived from 17 proceeded readily to give 19, which was hydrolyzed to produce 14a. Optically active (−)-14a was obtained through enzymatic hydrolysis. The racemic acid 14a was condensed with three representative chiral nucleophiles to give 14b—d. From the ^{1}H- and ^{19}F-NMR spectra of these derivatives, it was concluded that CFNA (14a) is potentially a much better CDA than the well-known α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA).

Key words chiral derivatizing agent; enantiomeric excess; CFPA; CFNA; MTPA; ^{19}F-NMR

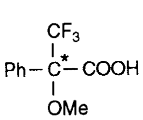
Among the various methods for analyzing the enantiomeric excess (ee) of chiral molecules, transformation of enantiomers into diastereomers with chiral derivatizing agents (CDAs) followed by NMR analysis occupies a prominent position.[2]) Of various nuclei susceptible to such analysis, the ^{19}F nucleus has many advantages over other nuclei such as ^{1}H, ^{13}C, ^{31}P, *etc.*, with regard to both sensitivity and resolution.[3]) We have been investigating a new CDA procedure using the above strategy based on the efficient reagent, α-cyano-α-fluorophenylacetic acid (CFPA, **1**).[4]) Despite many advantages[5,6]) over existing CDAs, including the much-used α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA, **2**),[7]) the CFPA method has not achieved general use, primarily because of the rather involved synthetic route to the reagent **1**.[1])

To overcome this problem we have attempted to prepare CFPA analogs that retain the inherent structural advantages[5]) of **1**, but which would be more readily crystallized, and consequently much easier to prepare, especially in the optically active form by fractional crystallization. Since the relative steric bulkiness of the three substituents on the α carbon of the acetate moiety has been optimized,[5]) we have undertaken small modifications, *i.e.*, *para*-substitution of the benzene ring of **1**, for ease of comparison. The basic strategy for the preparation of CFPA analogs **3** involves either nucleophilic fluorination (path *a*) or electrophilic fluorination (path *b*) as a key step, for which the readily available starting material is **4** or **5**, respectively (Chart 1).



$Ph-\overset{F}{\underset{CN}{C^{*}}}-COOH$

1 (CFPA)



$Ph-\overset{CF_3}{\underset{OMe}{C^{*}}}-COOH$

2 (MTPA)

We first focused on path *a*, which starts with the *para*-substituted benzaldehydes **4a—e**, taking into account the availability of starting materials, the ease of synthetic procedures, and the utility of conventional simple techniques for optical resolution. Thus, cyanohydrination of **4a—e** with Me_3SiCN/ZnI_2[8]) followed by nucleophilic fluorination with diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 produced **6a—e** in reasonable yield. Carboxylations of **6a—e** with CO_2/lithium *N*,*N*-diisopropylamide (LDA) in tetrahydrofuran (THF) at 0 °C afforded mainly complex mixtures and the target compounds **3a—e** were obtained in low yield (Chart 2). This result may be ascribed to the difficulty in generation of α-fluorocarbanions.[9])

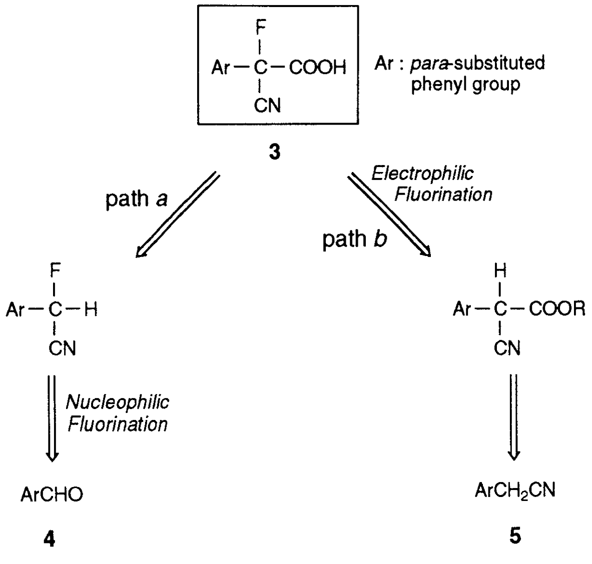


Chart 1. Basic Strategy for Preparation of CFPA Analogs **3**

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We next attempted an alternative route which involves fluorination after carboxyl group introduction (path *b*). Thus, benzyl cyanide derivatives **5b**—**e** were treated with NaH/$CO(OEt)_2$ to give the ethyl esters **7b**—**e** in good yield. These were subjected to electrophilic fluorination using $FClO_3$/NaH/THF[10)] to afford the CFPA ester analogs **10b**—**e** in high yield. Attempted saponification of **10b**—**e** with LiOH/THF/H_2O, however, gave the target compounds **3b**—**e** in poor yield, affording instead the decarboxylation compounds **6b**—**e** as the major products. This result may be due to the structural character of **3**, *i.e.*, ready decarboxylation under basic conditions. We next focused on the allyl ester derivatives **11b**—**e**. Reaction of **5b**—**e** with $CO(OCH_2CH=CH_2)_2$ gave **8b**—**e**, which were fluorinated with $FClO_3$ to give **11b**—**e** in good yield. However, $(PPh_3)_4Pd(0)$-catalyzed cleavage[11)] of the allyl esters **11b**—**e** yielded only complicated mixtures. We also prepared the benzyl ester analogs **12b**—**d** by $FClO_3$ fluorination of **9b**—**d**, in an analogous manner to the above. Hydrogenation of **12b**—**d** was attempted under various conditions to produce **3b**—**d**, again in unsatisfactory yields.

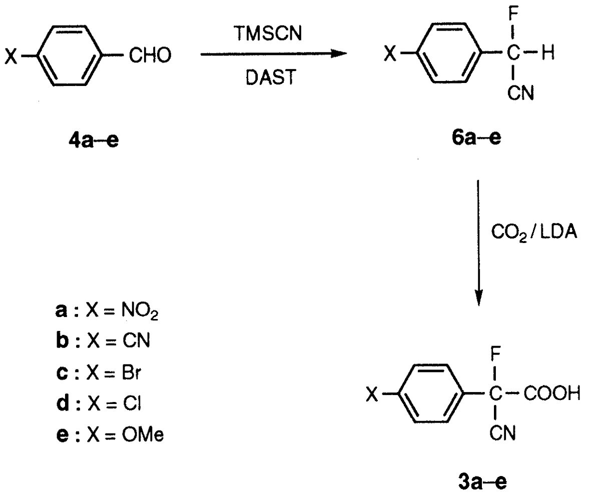


Chart 2

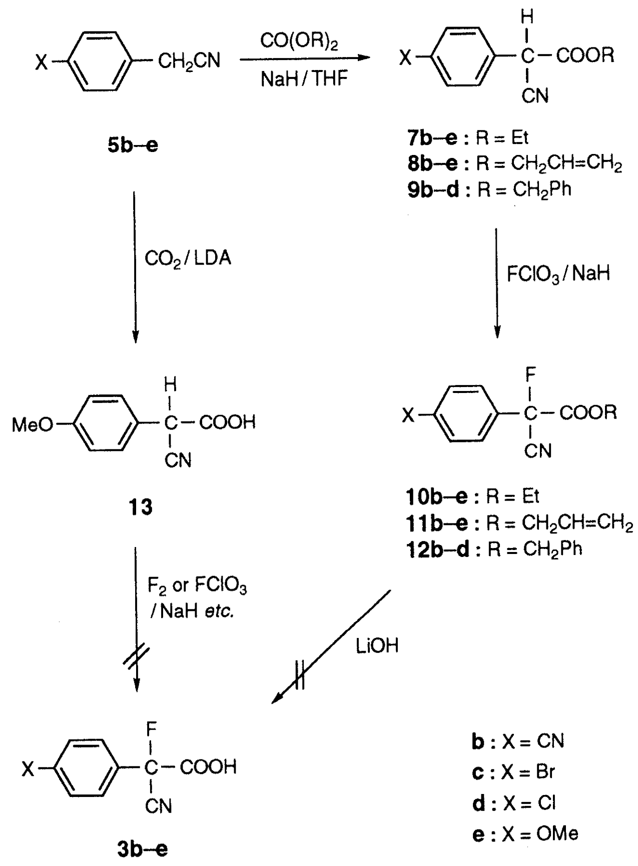


Chart 3

Since the approach to **3** from the corresponding esters **10**, **11**, or **12** did not give acceptable results, we next examined the route involving the direct fluorination of carboxylic acids so as to avoid the problematic step of ester cleavage. Thus, carboxylation of **5e** with CO_2/LDA/THF produced the malononitrile derivatives **13** in moderate yield. Electrophilic fluorination of **13** with $FClO_3$ or F_2 in the presence of various bases, however, did not afford the target acids **3e** (Chart 3).

Although there seemed room for improvement of the reaction conditions and there might be other *para*-substituted CFPA analogs that could be prepared by either of the synthetic pathways shown above, our immediate interest was to obtain a crystalline acid in an optically active form by simple fractional crystallization. Furthermore, the development of compounds which would give greater $\Delta\delta_F$ values than CFPA itself is strongly desirable. After examination of models of an ideal structure which would fit our purpose,[5)] we finally chose the naphthyl analog, α-cyano-α-fluoronaphthylacetic acid (CFNA, **14a**). We thought a bigger aryl substituent than the phenyl group would be necessary to enhance the population of a single, dominant rotamer after diastereomer formation and hence would bring about larger $\Delta\delta_F$ values between a pair of diastereomers than that of the corresponding CFPA diastereomers.[1)]

Cyanohydrination of the aldehyde **15** with NaCN followed by fluorination with DAST gave **16** in 45% yield. Carboxylation of **16** with CO_2 using various bases, however, did not produce **14a**. We finally investigated electrophilic fluorination. Treatment of **17** with $CO(OMe)_2$/NaH/THF produced the ester **18** in quantitative yield. Fluorination with $FClO_3$[10)] was applied to **18**, giving successfully **19** in excellent yield. Saponification of the methyl ester **19** with LiOH/THF/H_2O gave the desired acid **14a** in 79% yield, happily as a crystalline substance. Although the racemic acid **14a** forms diastereomeric salts with (−)-α-phenethylamine, it was found, to our disappointment, that the salts did not form crystals suitable for fractional recrystallization.

As a practical and readily available method for obtaining an optically active form of CFNA (**14a**), we investigated kinetic resolution by a biochemical method. Twenty commercially available hydrolytic enzymes were examined for enantioselective hydrolysis of the methyl ester **19** at 30 °C in a 0.1 M phosphate buffer (pH 7.0). The optical purity of the remaining ester was directly determined by HPLC with Chiralcel OJ (Daicel Chemical Co.). Among them, lipase F-AP15 (from *Rhizopus* sp., Amano Pharm. Co.) gave better enantiodifferentiation with an acceptable rate. Thus, the racemic ester (±)-**19** was resolved on a preparative scale by means of the

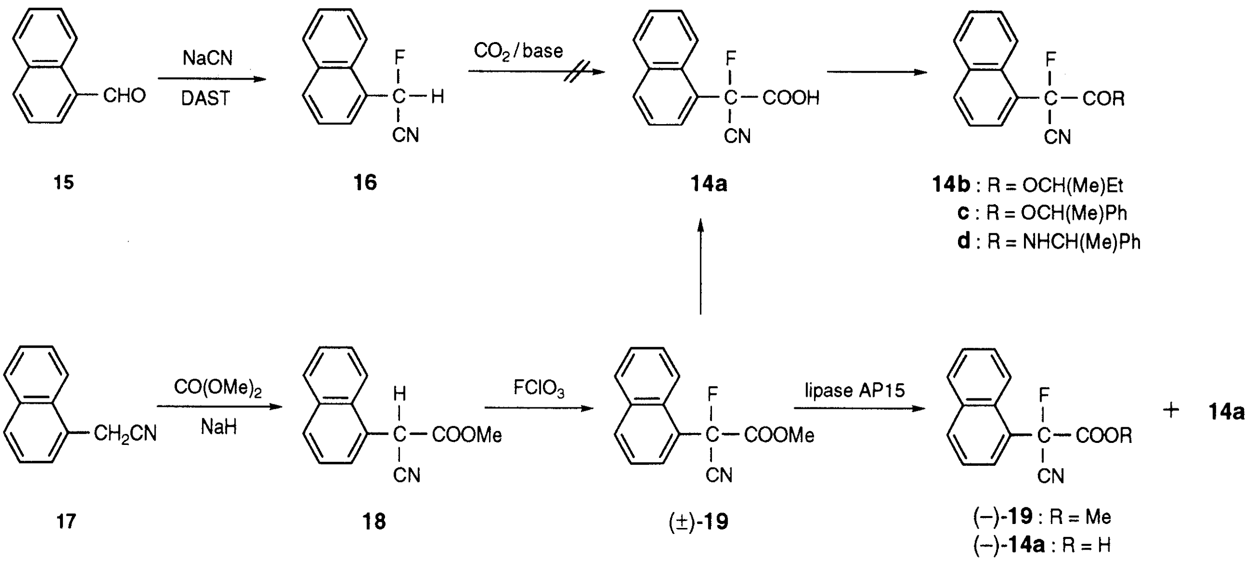
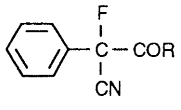
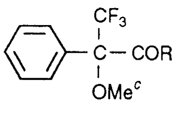
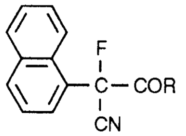


Chart 4

Table 1. ^{1}H Chemical Shift Difference $\Delta\delta_H$ (in ppm × 100) of Me Groups in Representative Diastereomers of **1**, **2**, and **14** by 270 MHz ^{1}H-NMR

R	 CFPA (**1**)		 MTPA (**2**)			 CFNA (**14**)	
Kind of Me proton	Me^a	Me^b	Me^a	Me^b	Me^c	Me^a	Me^b
OCH(Me^a)CH$_2$Me^b (**b**)	14.56	23.22	7.85	11.04	0.00	24.15	44.04
OCH(Me^a)Ph (**c**)	9.67	—	5.89	—	8.52	14.11	—
NHCH(Me^a)Ph (**d**)	8.01	—	4.04	—	4.03	3.44	—

following procedure. Lipase F-AP15 was added to an emulsion of the substrate in *N*,*N*-dimethylformamide (DMF) and a phosphate buffer, and the mixture was vigorously shaken at 30 °C for 7 h. After usual work-up, (−)-**19** of 99.3% ee and the acid **14a** were obtained in 21 and 65% yields, respectively. Hydrolysis of the resolved ester (−)-**19** with LiOH produced the corresponding acid (−)-**14a** in 83% yield (Chart 4).

The racemic acid **14a** was converted into representative derivatives, in order to examine preliminarily its resolution ability between a pair of diastereomers with NMR detection. Compound **14a** was treated with (COCl)$_2$ to give the chloride, which was reacted with *sec*-butyl alcohol, α-phenethyl alcohol, and α-phenethylamine, in the presence of pyridine, to give the corresponding CFNA diastereomers **14b**—**d**, respectively, in almost quantitative yield. The $\Delta\delta_H$ and $\Delta\delta_F$ values obtained from these diastereomers are summarized in Tables 1 and 2, respectively. From the comparison with the corresponding data[1] of both MTPA and CFPA diastereomers, we considered that CFNA (**14a**) would be potentially a much better reagent than MTPA (**2**), from the viewpoint of ee determination by the NMR method. However, contrary to our expectation, this naphthyl analog **14a** is not notably better for this task than CFPA (**1**).

Table 2. ^{19}F Chemical Shift Difference $\Delta\delta_F$ (in ppm × 100) of Three Representative Diastereomers of **1**, **2**, and **14** by 254 MHz ^{19}F-NMR

R	CFPA (**1**)	MTPA (**2**)	CFNA (**14**)
OCH(Me)Et (**b**)	24.0	0.0	17.4
OCH(Me)Ph (**c**)	104.7	20.3	7.2
NHCH(Me)Ph (**d**)	100.5	18.1	92.6

There is a need for the development of efficient CDAs, especially ones applicable for ee determination of chiral molecules "having remotely disposed stereogenic centers," considering the recent rapid progress in asymmetric and natural product syntheses. Although we have not succeeded in developing a new CDA, some significant information on both structural stability and the resolving ability of CFPA analogs was obtained. We are currently searching for better CDAs than the existing ones, especially from the practical viewpoint of ease of preparation of their optically active forms, so as to find a reagent that could be made available commercially at a reasonable price.

Experimental

General Notes Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 spectrometer. ^{1}H-NMR spectra were measured with Me_4Si as an internal standard and were recorded on a JEOL GX-270 (270 MHz) or a Varian Gemini 300 (300 MHz) spectrometer. ^{19}F-NMR spectra were measured with $CFCl_3$ as an internal standard and were taken with a JEOL GX-270 (254 MHz) spectrometer. Upfield shifts are quoted as negative δ values. EI mass spectra were taken with a JEOL JMS-D300 spectrometer. Column chromatography was performed on Kieselgel 60 (Merck, Art. 9385).

General Procedure for Preparation of α-Fluoro(*p*-substituted phenyl)acetonitrile Derivatives 6a—e A mixture of *p*-substituted benzaldehyde **4a—d** or **4e** (10 mmol), trimethylsilyl cyanide (TMSCN) (13 mmol), and zinc iodide (10 mg) was stirred at 30 °C for 1 h and diluted with dry CH_2Cl_2 (9 ml) in an ice-bath. To this solution was added slowly a solution of DAST in dry CH_2Cl_2 (9 ml) with stirring in an ice-bath and the resulting mixture was heated at reflux for 3 h, then poured into water (20 ml). The whole was stirred at room temperature for 1 h, then the organic layer was separated, washed successively with water, 0.5 N HCl, water, saturated $NaHCO_3$, and brine, and dried on $MgSO_4$. Evaporation of the solvent gave an oil, which was chromatographed on silica gel to afford **6a—d** or **6e** in 46—67% yield.

α-Fluoro(*p*-nitrophenyl)acetonitrile (6a) mp 31 °C. IR (KBr): 2254 (CN) cm^{-1}. ^1H-NMR δ: 6.24 (1H, d, $J_{HF}=46$ Hz, CH), 7.77 (2H, d, $J=7.5$ Hz, Ar), 8.38 (2H, d, $J=8.3$ Hz, Ar). ^{19}F-NMR δ: -175.8 (d, $J_{HF}=46$ Hz). MS *m/z*: 180 (M^+).

α-Fluoro(*p*-cyanophenyl)acetonitrile (6b) mp 44 °C. IR (KBr): 2255, 2229 (CN) cm^{-1}. ^1H-NMR δ: 6.16 (1H, d, $J_{HF}=47$ Hz), 7.68 (2H, d, $J=8$ Hz, Ar), 7.81 (2H, d, $J=8$ Hz, Ar). ^{19}F-NMR δ: -175.34 (d, $J_{HF}=47$ Hz). MS *m/z*: 160 (M^+), 141 (M^+-F), 102 (*p*-$NCPh^+$).

α-Fluoro(*p*-bromophenyl)acetonitrile (6c) IR (neat): 2252 (CN) cm^{-1}. ^1H-NMR δ: 6.03 (1H, d, $J_{HF}=47$ Hz, CH), 7.41—7.44 (2H, m, Ar), 7.64 (2H, d, $J=8$ Hz, Ar). ^{19}F-NMR δ: -168.9 (d, $J_{HF}=48$ Hz). MS *m/z*: 215 and 213 (M^+), 196 and 194 (M^+-F), 157 and 155 (*p*-$BrPh^+$).

α-Fluoro(*p*-chlorophenyl)acetonitrile (6d) IR (neat): 2252 (CN) cm^{-1}. ^1H-NMR δ: 6.04 (1H, d, $J_{HF}=47$ Hz, CH), 7.49 (4H, s, Ar). ^{19}F-NMR δ: -168.4 (d, $J_{HF}=48$ Hz). MS *m/z*: 171 and 169 (M^+).

α-Fluoro(*p*-methoxyphenyl)acetonitrile (6e) IR (neat): 2250 (CN) cm^{-1}. ^1H-NMR δ: 3.84 (3H, s, CH_3), 5.97 (1H, d, $J_{HF}=48$ Hz, CH), 6.97 (2H, d, $J=9$ Hz, Ar), 7.48 (2H, d, $J=9$ Hz, Ar). ^{19}F-NMR δ: -160.6 (d, $J_{HF}=48$ Hz). MS *m/z*: 146 (M^+), 134 (M^+-OMe), 58 (^+CHFCN).

Attempted Carboxylation of Fluoroacetonitrile Derivatives 6a—e with Carbon Dioxide BuLi (1.6 M in hexane, 50 mmol) was added to a solution of *N*,*N*-diisopropylamine (50 mmol) in THF (100 ml) at -78 °C and the mixture was stirred for 45 min. Then a fluoroacetonitrile derivative **6a—d** or **6e** (40 mmol) was added through a syringe and the whole was stirred at -78 °C for 45 min. Dried carbon dioxide was introduced into the solution at 0 °C for 30 min. The resulting solution was diluted with ether (50 ml) and extracted with saturated $NaHCO_3$ (50 ml × 3). The combined aqueous layer was acidified with concentrated HCl in an ice-bath and extracted with AcOEt (30 ml × 3). The organic layer was washed with brine and dried on $MgSO_4$. Evaporation of the solvent gave an oil, which was identified as a mixture of several products including **6a—d** or **6e** with less than 25% yield of the acid **3a—d** or **3e**, respectively.

General Procedure for Preparation of α-Cyanoarylacetic Esters 7b—e, 8b—e, 9b—d, and 18 Dimethyl, diethyl, diallyl, or dibenzyl carbonate (13 mmol) was added to a mixture of a *p*-substituted phenylacetonitrile **5b—e** or 1-naphthylacetonitrile **17** (10 mmol) and NaH (60% in mineral oil, 13 mmol) in dry THF (50 ml) by means of a syringe at 0 °C, and the mixture was heated at reflux for 4 h. The reaction was quenched with 1 N HCl (50 ml) and most of the THF was evaporated under reduced pressure. The remaining aqueous solution was extracted with AcOEt (30 ml × 3) and the extract was washed with brine and dried on $MgSO_4$. Evaporation of the solvent gave an oil, which was purified by silica gel column chromatography to afford the ester **7b—e**, **8b—e**, **9b—d**, or **18** in 61—95% yield.

Ethyl α-Cyano(*p*-cyanophenyl)acetate (7b) IR (neat): 2253, 2232 (CN), 1748 (CO) cm^{-1}. ^1H-NMR δ: 1.28 (3H, t, $J=7$ Hz, CH_3), 4.33 (2H, q, $J=7$ Hz, CH_2), 4.88 (1H, s, CH), 7.70 (2H, d, $J=8$ Hz, Ar), 7.90 (2H, d, $J=8$ Hz, Ar). MS *m/z*: 215 (M^+), 141 ($M^+-COOEt$).

Ethyl α-Cyano(*p*-bromophenyl)acetate (7c) IR (neat): 2253 (CN), 1745 (CO) cm^{-1}. ^1H-NMR δ: 1.25 (3H, t, $J=7$ Hz, CH_3), 4.15 (2H, q, $J=7$ Hz, CH_2), 4.75 (1H, s, CH), 7.36 (2H, d, $J=9$ Hz, Ar), 7.60 (2H, d, $J=9$ Hz, Ar). MS *m/z*: 269 and 267 (M^+), 196 and 194 ($M^+-COOEt$).

Ethyl α-Cyano(*p*-chlorophenyl)acetate (7d) IR (neat): 2254 (CN), 1747 (CO) cm^{-1}. ^1H-NMR δ: 1.29 (3H, t, $J=7.1$ Hz, CH_3), 4.26 (2H, q, $J=7.1$ Hz, CH_2), 4.70 (1H, s, CH), 7.41 (4H, s, Ar). MS *m/z*: 225 and 223 (M^+), 152 and 150 ($M^+-COOEt$).

Ethyl α-Cyano(*p*-methoxyphenyl)acetate (7e) IR (neat): 2251 (CN), 1743 (CO) cm^{-1}. ^1H-NMR δ: 1.27 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 3.83 (3H, s, OCH_3), 4.15 (2H, q, $J=7$ Hz, CH_2), 4.70 (1H, s, CH), 6.96 (2H, d, $J=9$ Hz, Ar), 7.46 (2H, d, $J=9$ Hz, Ar). MS *m/z*: 219 (M^+), 146 ($M^+-COOEt$).

Allyl α-Cyano(*p*-cyanophenyl)acetate (8b) IR (neat): 2253, 2232 (CN), 1750 (CO) cm^{-1}. ^1H-NMR δ: 4.67—4.87 (2H, m, OCH_2), 4.92 (1H, s, ArCH), 5.20—5.57 (2H, m, $CH=C\underline{H}_2$), 5.70—6.23 (1H, m, $C\underline{H}=CH_2$), 7.70 (2H, d, $J=8$ Hz, Ar), 7.90 (2H, d, $J=8$ Hz, Ar). MS *m/z*: 226 (M^+), 141 ($M^+-COOCH_2CH=CH_2$).

Allyl α-Cyano(*p*-bromophenyl)acetate (8c) IR (neat): 2253 (CN), 1748 (CO) cm^{-1}. ^1H-NMR δ: 4.70 (2H, d, $J=5$ Hz, OCH_2), 4.75 (1H, s, ArCH), 5.12—6.20 (3H, m, $CH=CH_2$), 7.35 (2H, d, $J=7$ Hz, Ar), 7.60 (2H, d, $J=7$ Hz, Ar). MS *m/z*: 281 and 279 (M^+), 196 and 194 ($M^+-COOCH_2CH=CH_2$).

Allyl α-Cyano(*p*-chlorophenyl)acetate (8d) IR (neat): 2254 (CN), 1749 (CO) cm^{-1}. ^1H-NMR δ: 4.66—4.69 (2H, m, OCH_2), 4.76 (1H, s, ArCH), 5.25—5.34 (2H, m, $CH=C\underline{H}_2$), 5.80—5.93 (1H, m, $C\underline{H}=CH_2$), 7.41 (4H, s, Ar). MS *m/z*: 237 and 235 (M^+), 152 and 150 ($M^+-COOCH_2CH=CH_2$).

Allyl α-Cyano(*p*-methoxyphenyl)acetate (8e) IR (neat): 2251 (CN), 1749 (CO) cm^{-1}. ^1H-NMR δ: 3.83 (3H, s, CH_3), 4.70 (2H, d, $J=5$ Hz, OCH_2), 4.75 (1H, s, CH), 5.10—6.20 (3H, m, $CH=CH_2$), 7.00 (2H, d, $J=9$ Hz, Ar), 7.50 (2H, d, $J=9$ Hz, Ar). MS *m/z*: 231 (M^+), 146 ($M^+-COOCH_2CH=CH_2$).

Benzyl α-Cyano(*p*-cyanophenyl)acetate (9b) mp 101 °C. IR (KBr): 2255, 2232 (CN), 1748 (CO) cm^{-1}. ^1H-NMR δ: 4.87 (1H, s, CH), 5.27 (2H, s, CH_2), 7.40 (5H, m, Ar), 7.58 (2H, d, $J=9$ Hz, Ar), 7.83 (2H, d, $J=9$ Hz, Ar). MS *m/z*: 276 (M^+), 141 ($M^+-COOBn$).

Benzyl α-Cyano(*p*-bromophenyl)acetate (9c) mp 79 °C. IR (KBr): 2255 (CN), 1748 (CO) cm^{-1}. ^1H-NMR δ: 4.73 (1H, s, CH), 5.23 (2H, s, CH_2), 7.25—7.53 (9H, m, Ar). MS *m/z*: 331 and 329 (M^+), 196 and 194 ($M^+-COOBn$).

Benzyl α-Cyano(*p*-chlorophenyl)acetate (9d) mp 71 °C. IR (KBr): 2258 (CN), 1749 (CO) cm^{-1}. ^1H-NMR δ: 4.74 (1H, s, CH), 5.20 (2H, s, CH_2), 7.26—7.38 (9H, m, Ar). MS *m/z*: 287 and 285 (M^+), 152 and 150 ($M^+-COOBn$).

Benzyl α-Cyano(*p*-methoxyphenyl)acetate (9e) IR (neat): 1749 (CO) cm^{-1}. ^1H-NMR δ: 3.81 (3H, s, CH_3), 4.69 (2H, s, CH_2), 5.19 (1H, s, CH), 6.90 (2H, d, $J=9$ Hz, Ar), 7.33 (2H, d, $J=9$ Hz, Ar) 7.37 (5H, s, Ar). MS *m/z*: 281 (M^+), 146 ($M^+-COOBn$).

Methyl α-Cyano(1-naphthyl)acetate (18) mp 85 °C. IR (KBr): 2257 (CN), 1750 (CO) cm^{-1}. ^1H-NMR δ: 3.80 (3H, s, CH_3), 5.40 (1H, s, CH), 7.40—8.17 (7H, m, Ar). MS *m/z*: 225 (M^+), 166 ($M^+-COOCH_3$).

General Procedure for Preparation of α-Cyano-α-fluoro(*p*-substituted phenyl)acetic Esters 10b—e, 11b—e, 12b—d, and 19 Gaseous $FClO_3$ was introduced into a solution of α-cyanoarylacetonitrile **7b—e**, **8b—e**, **9b—d**, or **18** (10 mmol) and NaH (60% in mineral oil, 13 mmol) in dry THF (50 ml) for 2 h, according to the procedure previously reported.[10] The resulting solution was diluted with ether (50 ml) and insoluble materials were removed by filtration. Concentration of the filtrate gave the fluorinated product **10b—e**, **11b—e**, **12b—d**, or **19** in 48—95% yield.

Ethyl α-Cyano-α-fluoro(*p*-cyanophenyl)acetate (10b) IR (neat): 2254, 2234 (CN), 1774 (CO) cm^{-1}. ^1H-NMR δ: 1.33 (3H, t, $J=7.1$ Hz, CH_3), 4.29—4.47 (2H, m, CH_2), 7.41—7.80 (4H, m, Ar). ^{19}F-NMR δ: -151.0 (s). MS *m/z*: 233 (M^++1), 206 (M^+-CN), 159 ($M^+-COOEt$).

Ethyl α-Cyano-α-fluoro(*p*-bromophenyl)acetate (10c) IR (neat): 1774 (CO) cm^{-1}. ^1H-NMR δ: 1.31 (3H, t, $J=7.3$ Hz, CH_3), 4.26—4.44 (2H, m, CH_2), 7.52 (2H, d, $J=8.3$ Hz, Ar), 7.64 (2H, d, $J=8.3$ Hz, Ar). ^{19}F-NMR δ: -147.62 (s). MS *m/z*: 287 and 285 (M^+), 268 and 266 (M^+-F), 261 and 258 (M^+-CN), 214 and 212 ($M^+-COOEt$).

Ethyl α-Cyano-α-fluoro(*p*-chlorophenyl)acetate (10d) IR (neat): 2253 (CN), 1747 (CO) cm^{-1}. ^1H-NMR δ: 1.31 (3H, t, $J=7.1$ Hz, CH_3), 4.29—4.44 (2H, m, CH_2), 7.47 (2H, d, $J=8.3$ Hz, Ar), 7.60 (2H, d, $J=8.5$ Hz, Ar). ^{19}F-NMR δ: -147.1 (s). MS *m/z*: 244 and 242 (M^++1), 224 and 222 (M^+-F), 217 and 215 (M^+-CN), 170 and 168 ($M^+-COOEt$).

Ethyl α-Cyano-α-fluoro(*p*-methoxyphenyl)acetate (10e) IR (neat): 2253 (CN), 1773 (CO) cm^{-1}. ^1H-NMR δ: 1.25 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 3.85 (3H, s, OCH_3), 4.23 (2H, q, $J=7$ Hz, CH_2), 7.00 (2H, d, $J=8$ Hz, Ar), 7.63 (2H, d, $J=8$ Hz, Ar). MS *m/z*: 237 (M^+), 164 ($M^+-COOEt$).

Allyl α-Cyano-α-fluoro(*p*-cyanophenyl)acetate (11b) IR (neat): 2255,

2234 (CN), 1779 (CO) $\mathrm{cm^{-1}}$. ^{1}H-NMR δ: 4.71—4.84 (2H, m, OCH$_2$), 5.31—5.37 (2H, m, CH$=$C$\underline{\mathrm{H}}_2$), 5.77—5.93 (1H, m, CH), 7.77—7.84 (4H, m, Ar). ^{19}F-NMR δ: -151.0 (s). MS *m*/*z*: 245 ($\mathrm{M^+}+1$), 218 ($\mathrm{M^+}-$CN), 159 ($\mathrm{M^+}-$COOCH$_2$CH$=$CH$_2$).

Allyl α-Cyano-α-fluoro(*p*-bromophenyl)acetate (11c) IR (neat): 2254 (CN), 1776 (CO) $\mathrm{cm^{-1}}$. ^{1}H-NMR δ: 4.69—4.83 (2H, m, OCH$_2$), 5.29—5.36 (2H, m, CH$=$C$\underline{\mathrm{H}}_2$), 5.79—5.91 (1H, m, CH), 7.52 (2H, d, $J=8.3$ Hz, Ar), 7.64 (2H, d, $J=8.3$ Hz, Ar). ^{19}F-NMR δ: -147.5 (s); MS *m*/*z*: 299 and 297 ($\mathrm{M^+}$), 212 and 214 ($\mathrm{M^+}-$COOCH$_2$CH$=$CH$_2$).

Allyl α-Cyano-α-fluoro(*p*-chlorophenyl)acetate (11d) IR (neat): 2254 (CN), 1777 (CO) $\mathrm{cm^{-1}}$. ^{1}H-NMR δ: 4.70—4.83 (2H, m, OCH$_2$), 5.29—5.35 (2H, m, CH$=$C$\underline{\mathrm{H}}_2$), 5.79—5.94 (1H, m, CH), 7.50—7.76 (4H, m, Ar). ^{19}F-NMR δ: -146.9 (s). MS *m*/*z*: 255 and 253 ($\mathrm{M^+}+1$), 229 and 227 ($\mathrm{M^+}-$CN), 170 and 168 ($\mathrm{M^+}-$COOCH$_2$CH$=$CH$_2$).

Allyl α-Cyano-α-fluoro(*p*-methoxyphenyl)acetate (11e) IR (neat): 2254 (CN), 1774 (CO) $\mathrm{cm^{-1}}$. ^{1}H-NMR δ: 3.83 (3H, s, CH$_3$), 4.80 (2H, d, $J=7$ Hz, OCH$_2$), 5.07—6.01 (3H, m, CH$_2$$=$CH), 6.98 (2H, d, $J=9$ Hz, Ar), 7.60 (2H, d, $J=9$ Hz, Ar). MS *m*/*z*: 249 ($\mathrm{M^+}$), 164 ($\mathrm{M^+}-$COOCH$_2$CH$=$CH$_2$).

Benzyl α-Cyano-α-fluoro(*p*-cyanophenyl)acetate (12b) mp 52 °C. IR (KBr): 2256, 2233 (CN), 1764 (CO) $\mathrm{cm^{-1}}$. ^{1}H-NMR δ: 5.30 (2H, s, CH$_2$), 7.31—7.38 (5H, m, Ar), 7.67—7.89 (4H, m, Ar). ^{19}F-NMR δ: -151.1 (s); MS *m*/*z*: 294 ($\mathrm{M^+}$), 159 ($\mathrm{M^+}+$COOBn).

Benzyl α-Cyano-α-fluoro(*p*-bromophenyl)acetate (12c) IR (neat): 1737 (CO) $\mathrm{cm^{-1}}$. ^{1}H-NMR δ: 5.50 (2H, s, CH$_2$), 7.30—7.61 (9H, m, Ar). MS *m*/*z*: 324 and 322 ($\mathrm{M^+}-$CN).

Benzyl α-Cyano-α-fluoro(*p*-chlorophenyl)acetate (12d) IR (neat): 2254 (CN), 1777 (CO) $\mathrm{cm^{-1}}$. ^{1}H-NMR δ: 5.27 (2H, s, CH$_2$), 7.23—7.53 (9H, m, Ar). ^{19}F-NMR δ: -146.9 (s). MS *m*/*z*: 305 and 303 ($\mathrm{M^+}$), 170 and 168 ($\mathrm{M^+}-$COOBn).

Methyl α-Cyano-α-fluoro-(1-naphthyl)acetate (19) mp 57 °C. IR (KBr): 2254 (CN), 1774 (CO) $\mathrm{cm^{-1}}$. ^{1}H-NMR δ: 3.85 (3H, s, CH$_3$), 7.51—7.63 (3H, m, Ar), 7.90—8.02 (3H, m, Ar), 8.19 (1H, d, $J=6.5$ Hz, Ar). ^{19}F-NMR δ: -143.0 (s). MS *m*/*z*: 243 ($\mathrm{M^+}$), 184 ($\mathrm{M^+}-$COOCH$_3$).

Attempted Saponification of the Ethyl Esters 10b—e A 1 N LiOH solution (5 ml) was added to a stirred mixture of the ethyl ester **10b—d** or **10e** (1 mmol) in THF (10 ml) and H$_2$O (10 ml), and the whole was stirred at room temperature for 5—30 min with monitoring by TLC. Most of the THF was evaporated under reduced pressure and the resulting aqueous solution was washed with ether (10 ml), acidified with 1 N HCl in an ice-bath, and extracted with AcOEt (20 ml × 3). The extract was washed with a small amount of brine and dried on MgSO$_4$. Evaporation of the solvent gave an oil, which was identified from the NMR spectra as a mixture of mainly the decarboxylation product **6b—d** or **6e** and a small amount of **3b—d** or **3e**, respectively.

Attempted Ester Cleavage of the Allyl Esters 11b—e Morpholine (174 μl, 2 mmol) and tetrakis(triphenylphosphine)palladium (0) (12 mg, 0.01 mmol) were added to a solution of the allyl ester **11b—d** or **11e** (1 mmol) in THF (10 ml) at 0 °C, and the whole mixture was stirred at 0 °C for 30 min. Evaporation of the solvent gave an oil, which was dissolved in 1 N NaOH (10 ml) and washed with ether (10 ml). The aqueous solution was acidified with 1 N HCl in an ice-bath and extracted with AcOEt (20 ml × 3). The extract was washed with a small amount of brine and dried on MgSO$_4$. Evaporation of the solvent gave an oil, which was identified from the NMR spectra as a complex mixture of products.

Attempted Hydrogenolysis of the Benzyl Esters 12b—d A mixture of the benzyl ester **12b—d** or **12e** (1 mmol) and 5% Pd–C (100 mg) in MeOH (10 ml) was stirred under hydrogen (1 atm) at room temperature for 2 h. The resulting mixture was filtered and the filtrate was concentrated to give an oil, which was identified from the NMR spectra as a mixture of mainly the decarboxylation product **6b—d** or **6e** and a small amount of **3b—d** or **3e**, respectively.

Preparation of the α-Cyano(*p*-methoxyphenyl)acetic Acid 13 A mixture of diisopropylamine (6.36 ml, 45.5 mmol) in THF (100 ml) was treated with BuLi (1.6 M in hexane, 26.3 ml, 42 mmol) at -78 °C, and the reaction mixture was stirred at -20 °C for 30 min. It was then rechilled at -78 °C and a solution of the *p*-methoxybenzylcyanide **5e** (4.74 ml, 35 mmol) in THF (10 ml) was added by means of a syringe. The solution was stirred for 30 min, then dried CO$_2$ was introduced at 0 °C for 15 min. Ether (200 ml) was added and the mixture was extracted with saturated NaHCO$_3$ (100 ml × 3). The aqueous solution was acidified with concentrated HCl and extracted with AcOEt (100 ml × 3). The extract was washed with brine and dried on MgSO$_4$. Evaporation of the solvent gave a colorless solid which was recrystallized from hexane–acetone to give 5.14 g (76%) of α-cyano(*p*-methoxyphenyl)acetic acid **13** as colorless needles. mp 92—93 °C. IR (KBr): 3553 (OH), 2260 (CN), 1725 (CO) $\mathrm{cm^{-1}}$. ^{1}H-NMR δ: 3.88 (3H, s, CH$_3$), 4.73 (1H, s, CH), 5.67 (1H, s, COOH), 7.00 (2H, d, $J=9$ Hz, Ar), 7.46 (2H, d, $J=9$ Hz, Ar). MS *m*/*z*: 191 ($\mathrm{M^+}$), 108 (*p*-MeOPh$^+$).

Attempted Fluorination of Cyanoacetic Acid 13 A mixture of diisopropylamine (0.48 ml, 3.4 mmol) in THF (20 ml) was treated with BuLi (1.6 M in hexane, 2.1 ml, 3.3 mmol) at -78 °C and the reaction mixture was stirred at -20 °C for 45 min. It was rechilled to -78 °C and a solution of the cyanoacetic acid **13** (287 mg, 1.5 mmol) in THF (5 ml) was added by means of a syringe. The whole was stirred at room temperature for 40 min, then FClO$_3$ gas was introduced into the solution for 2 h, according to the procedure previously reported.[10] The resulting solution was diluted with ether (50 ml) and insoluble materials were removed by filtration. Concentration of the filtrate gave the starting material **13** (262 mg, 83% recovered).

Preparation of Fluoro(1-naphthyl)acetonitrile 16 Saturated NaHSO$_3$ (20 ml) was slowly added to a stirred mixture of 1-naphthylaldehyde **15** (7.8 g, 0.05 mol) and NaCN (2.45 g, 0.05 mol) in H$_2$O (10 ml) over a period of 1 h below 10 °C in an ice-bath. The resulting mixture was extracted with ether (50 ml × 3). The combined extract was washed with brine and dried on MgSO$_4$. Evaporation of the solvent gave the cyanohydrin as a brown oil (7.0 g, 75%). A solution of the crude cyanohydrin (5.49 g, 0.03 mol) in CH$_2$Cl$_2$ (100 ml) was treated dropwise with DAST (3.96 ml, 0.03 mol) at -80 °C under a nitrogen atmosphere and the mixture was stirred at 0 °C for 1 h. It was poured into saturated Na$_2$CO$_3$ (50 ml) and the organic layer was separated, washed with H$_2$O and dried on MgSO$_4$. Evaporation of the solvent gave a brown oil, which was chromatographed on silica gel to produce fluoro(1-naphthyl)acetonitrile **16** as a brown oil (3.3 g, 60%). IR (neat): 2252 (CN) $\mathrm{cm^{-1}}$. ^{1}H-NMR δ: 6.66 (1H, d, $J_{\mathrm{HF}}=47$ Hz, CH), 7.5—8.1 (7H, m, Ar). ^{19}F-NMR δ: -169.9 (d, $J_{\mathrm{HF}}=48$ Hz). MS *m*/*z*: 185 ($\mathrm{M^+}$), 166 ($\mathrm{M^+}-$F).

Preparation of Methyl α-Cyano-α-fluoro(1-naphthyl)acetate (−)-19 An emulsion was prepared by pouring a DMF solution (3 ml) of (±)-**19** (100 mg) into a 0.1 M phosphate buffer (30 ml, pH 7.0), then a suspension of lipase F-AP15 (500 mg, Amano Pharm. Co.) in the same buffer (20 ml) was added and the resulting suspension was vigorously shaken at 30 °C for 7h. After addition of acetone (150 ml), the mixture was left standing at room temperature for 7 h. Insoluble materials were filtered off and the filtrate was concentrated. The residual material was extracted with AcOEt (30 ml × 3) and dried on MgSO$_4$. Evaporation of the solvent gave an oil, which was chromatographed on silica gel to afford 21 mg (21%) of the optically active ester (−)-**19** of ee 99.3% (as checked by HPLC using Chiralcel OJ) and 61 mg (65%) of almost racemized acid **14a**. Spectral data of (−)-**19**: $[\alpha]_{\mathrm{D}}^{23}$ $-21.4°$ ($c=0.63$, CHCl$_3$). IR (neat): 2254 (CN), 1774 (CO) $\mathrm{cm^{-1}}$. ^{1}H-NMR δ: 3.85 (3H, s, CH$_3$), 7.5—8.2 (7H, m, Ar). ^{19}F-NMR δ: -143.0 (s). MS *m*/*z*: 243 ($\mathrm{M^+}$), 184 ($\mathrm{M^+}-$COOMe).

Preparation of α-Cyano-α-fluoro(1-naphthyl)acetic Acid (−)-14a A 1 N LiOH solution (1 ml) was added to a stirred mixture of the methyl ester (−)-**19** (45 mg, 0.185 mmol) in THF (2.5 ml) and H$_2$O (2.5 ml), and the whole was stirred at room temperature for 5 min. Most of the THF was evaporated under reduced pressure and the resulting aqueous solution was washed with ether (2 ml), acidified with 1 N HCl in an ice-bath, and extracted with AcOEt (5 ml × 3). The extract was washed with a small amount of brine and dried on MgSO$_4$. Evaporation of the solvent gave 35 mg (83%) of (−)-**14a** as colorless crystals. mp 129 °C. $[\alpha]_{\mathrm{D}}^{27}$ $-8.1°$ ($c=1.00$, CHCl$_3$). IR (KBr): 3400 (OH), 1783 (CO) $\mathrm{cm^{-1}}$. ^{1}H-NMR δ: 7.5—8.2 (8H, m, Ar and COOH). ^{19}F-NMR δ: -143.6 (s); MS *m*/*z*: 229 ($\mathrm{M^+}$), 185 ($\mathrm{M^+}-$CO$_2$), 184 ($\mathrm{M^+}-$COOH), 166 ($\mathrm{M^+}-$CO$_2-$F).

Preparation of α-Cyano-α-fluoro(1-naphthyl)acetic Acid Derivatives 14b—d The representative diastereomeric derivatives **14b—d** were prepared according to the general procedure previously reported.[1]

2-Butyl α-Cyano-α-fluoro(1-naphthyl)acetates (14b) IR (neat): 2361 (CN), 1768 (CO), 1601 (Ar), 1252 (C-O-C) $\mathrm{cm^{-1}}$. ^{1}H-NMR δ: 0.35 and 0.80 ($\Delta\delta=0.44$) (3H, t, $J=7.5$ Hz, CH$_2$C$\underline{\mathrm{H}}_3$), 0.95 and 1.19 ($\Delta\delta=0.24$) (3H, d, $J=6.1$ Hz, CHC$\underline{\mathrm{H}}_3$), 1.32 and 1.52 ($\Delta\delta=0.20$) (2H, m, CH$_2$), 4.89 (1H, m, CH), 7.4—8.2 (7H, m, Ar). ^{19}F-NMR δ: -142.9 and -142.7 ($\Delta\delta=0.1735$) (s). MS *m*/*z*: 285 ($\mathrm{M^+}$), 184 ($\mathrm{M^+}-$COOCH(Me)Et), 165 ($\mathrm{M^+}-$COOCH(Me)Et$-$F), 158 ($\mathrm{M^+}-$COOCH(Me)Et$-$CN), 57 (EtCH(Me)$^+$).

1-Phenethyl α-Cyano-α-fluoro(1-naphthyl)acetates (14c) IR (neat): 2341 (CN), 1771 (CO), 1602 (Ar), 1245 (C–O–C) $\mathrm{cm^{-1}}$. ^{1}H-NMR δ: 1.39

and 1.53 ($\Delta\delta = 0.14$) (3H, d, $J = 6.6$ Hz, CH_3), 5.96 (1H, m, CH), 6.8—8.2 (12H, m, Ar). ^{19}F-NMR δ: -143.0 and -142.9 ($\Delta\delta = 0.0723$) (s). MS *m*/*z*: 333 (M^+), 184 ($M^+ - COOCH(Me)Ph$), 165 ($M^+ - COOCH(Me)Ph - F$), 158 ($M^+ - COOCH(Me)Ph - CN$), 105 ($PhCH(Me)^+$).

***N*-(1-Phenethyl)-α-cyano-α-fluoro(1-naphthyl)acetates (14d)** mp 116—134 °C. IR (KBr): 3285 (NH), 2365 (CN), 1677 (CO) cm^{-1}. ^{1}H-NMR δ: 1.54 and 1.58 ($\Delta\delta = 0.03$) (3H, d, $J = 7.1$ Hz, CH_3), 5.21 (1H, m, CH), 6.74 and 6.84 ($\Delta\delta = 0.11$) (1H, d, $J = 7.1$ Hz, NH), 7.2—8.3 (12H, m, Ar). ^{19}F-NMR δ: -140.0 and -138.9 ($\Delta\delta = 0.9257$) (s). MS *m*/*z*: 332 (M^+), 184 ($M^+ - CONHCH(Me)Ph$), 165 ($M^+ - CONHCH(Me)Ph - F$), 158 ($M^+ - CONHCH(Me)Ph - CN$), 105 ($PhCH(Me)^+$).

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