Synthesis and Optical Resolution of 2-Aryl-2-fluoropropionic Acids, Fluorinated Analogues of Non-steroidal Anti-inflammatory Drugs (NSAIDs)

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We report the synthesis of optically active 2-aryl-2-fluoropropionic acids 2 as non-epimerizable mimics of 2-arylpropionic acids 1, a class of compounds which have been widely used as non-steroidal anti-inflammatory drugs (NSAIDs). This is a continuation of our research involving the design, synthesis, and evaluation of chiral fluorine-containing organic molecules as effective analogues of pharmacologically important compounds.

Key words 2-aryl-2-fluoropropionic acid; isostere; non-steroidal anti-inflammatory drug; α-fluorination; perchloryl fluoride

2-Arylpropionic acids **1** are used clinically as non-steroidal anti-inflammatory drugs (NSAIDs) (Fig. 1). The (*S*)-enantiomers have been considered to be pharmacologically more active than the (*R*)-enantiomers of these acids.[1)] Nonetheless, these agents are normally marketed as racemates. This is possible because it has been shown[1—4)] that an *in vivo* inversion at the stereogenic center converts the pharmacologically less active (*R*)-enantiomers into the more active (*S*)-enantiomers, thereby obviating a prior separation of enantiomers.

Owing to this *in vivo* epimerization, it is difficult to examine and clarify the medicinal actions or metabolism of each enantiomer closely. The replacement of hydrogen with fluorine can produce isosteric analogues (pseudologues) that often mimic the parent with respect to biological behavior. Therefore, to provide tools to study the *in vivo* behavior of the individual enantiomers of these NSAIDs, we have prepared a series of chiral non-epimerizable 2-fluorinated 2-arylpropionic acids **2** (Fig. 2).

Some other groups have reported the synthesis of 2-aryl-2-fluoropropionic acid derivatives **2a**, **b**, and **4a** (R=Me) by nucleophilic fluorination of the corresponding 2-hydroxy acids or 2-aryl epoxides with (diethylamino)sulfur trifluoride (DAST) or $Et_3N \cdot 3HF$, respectively (Eqs. 1, 2),[5,6)] or electrophilic fluorination of the enol silyl ether of **3a** with acetyl hypofluorite (Eq. 3).[7)] Laurent *et al.* reported the synthesis of 2-fluorinated ester **4a** (R=Et) by electrochemical oxidation in fluorinating media (Eq. 4).[8)] However, all of these methods require rather delicate conditions and/or many steps, and therefore, they lack synthetic generality (Chart 1).

In this paper, we report an efficient and practical synthesis of 2-aryl-2-fluoropropionic acids **2** by direct fluorination of readily available 2-arylpropionic acid methyl esters **3** with diluted perchloryl fluoride ($FClO_3$), according to the convenient procedure we have reported previously.[9—11)] A simple and general procedure for optical resolution of the 2-fluoro acids **2** is also described.

Results and Discussion

We first attempted direct fluorination of carbanions derived from methyl ester **3a** using selectfluor[12)] and *N*-fluorobenzenesulfonimide.[13)] However, the yields seemed sensitive to the amount and kind of bases employed for the reaction and the results were found not to be reproducible. We then focused on fluorination using diluted $FClO_3$,[9—11)] considering the successful results obtained in the preparation of the structurally similar 2-cyano-2-fluoro-*p*-tolylacetic acid ethyl ester.[14,15)]

We first examined bases and temperatures for the fluorination of ibuprofen methyl ester **3a** with $FClO_3$ in order to optimize reaction conditions (Table 1). The best result was obtained when a solution of the lithium enolate of **3a** in tetrahydrofuran (THF), formed by treatment with lithium diisopropylamide (LDA) by usual procedure, was subjected to slow introduction of diluted $FClO_3$, at −40 °C for 1 h, to give α-fluoroibuprofen methyl ester **4a** in 93% yield (entry 10).

We then applied this fluorination procedure to the methyl esters of other NSAIDs **3b**—**e**, which are readily prepared from the corresponding commercially available acids **1b**—**e**. In the case of **3b**—**d** the corresponding α-fluoro esters **4b**—**d** were obtained in excellent yields. In the case of **3e**, however, formation of a complex mixture was observed. Since

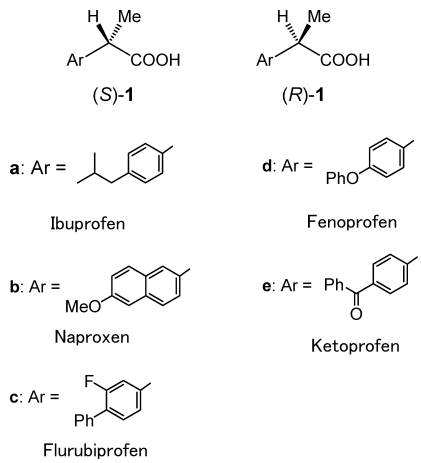

Fig. 1. Structures of 2-Arylpropionic Acids

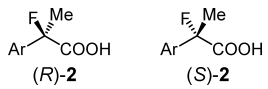

Fig. 2. Structures of 2-Aryl-2-fluoropropionic Acids

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the ketone **3e** was used without protection an intermolecular condensation may be the reason for the formation of side products. In order to avoid this complication, ketone **3e** was treated with ethylene glycol to give the corresponding acetal **5**. This was subjected to our fluorination procedure to afford the α-fluoro ester **6** in 79% yield. Treatment of **6** with aqueous HCl gave **4e** in good yield. Saponification of the α-fluoro esters **4a**—**e** with aqueous KOH successfully produced α-fluoro acids **2a**—**e** in good yields with no evidence of any defluorination (Chart 2).

Having the non-epimerizable pseudologues **2a**—**e** in hand, we next considered procedures for optical resolution. Since attempted resolution using chiral aminoindanol[16] or menthol as chiral auxiliaries was unsuccessful, we turned our attention to the use of (−)-carenediol (**7**).[17]

Racemic 2-aryl-2-fluoropropionic acids **2a**—**e** were treated with $(COCl)_2$ to give the chlorides, which were condensed with (−)-carenediol (**7**) to afford the corresponding pairs of ester diastereomers **8a**—**e** and **9a**—**e**, respectively. These diastereomeric esters were easily separated by column chromatography on silica gel (hexane/AcOEt=4/1 or $CHCl_3$/AcOEt=95/5) to yield the less polar esters **8a**—**e** and the more polar esters **9a**—**e** in moderate yields. Hydrolysis of each of **8a**—**e** and **9a**—**e** with aqueous KOH produced (−)-**2a**—**e** and (+)-**2a**—**e**, respectively (Chart 3).

Absolute configuration of (−)-**2a** ($[\alpha]_D^{27}$ −27.1°, c=1.1, EtOH) was determined as *R* by comparison with the data of literature ($[\alpha]_D^{24}$ −22.6°, c=1.2, EtOH).[5] The diastereomers, **9b**, **8c**, and **8e**, were recrystallized from hexane/AcOEt or hexane/$CHCl_3$ to give single crystals that were suitable for X-ray crystallographic analysis. The X-ray data showed the absolute configurations of (+)-**2b**, (−)-**2c**, and (−)-**2e** to be *S*, *R*, and *R*, respectively. In the case of **2d**, however, neither of the diastereomers **8d** and **9d** could be crystallized. Thus, (−)-**2d** was treated with (*S*)-(−)-α-phenethylamine in $CHCl_3$ to give the crystalline salt, of which X-ray analysis showed that (−)-**2d** has the *R* configuration. Thus, all the (−)-acids **2a**—**e** proved to have *R* absolute configurations.

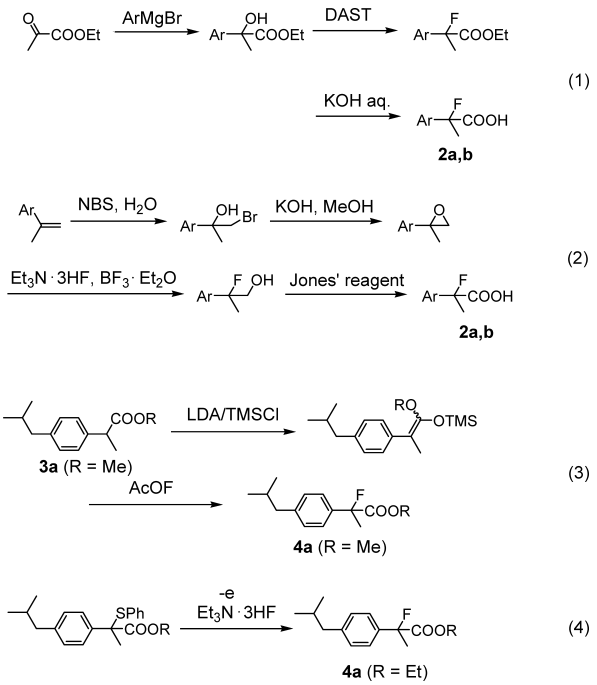
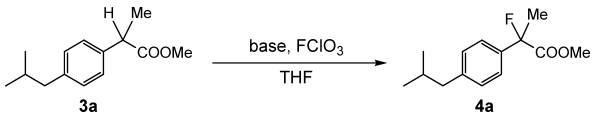


Chart 1

Conclusion

We have developed a simple procedure for preparation of

Table 1. Fluorination of Methyl Ester of Ibuprofen



Entry	Base	Temperature	Time	Product[a]
1	NaH (1.2 eq)	rt	2 h	SM recovery
2	KH (1.5 eq)	rt	1 h	SM recovery
3	*t*-BuOK (1.2 eq)	rt	1 h	Complex mixture
4	NHMDS (1.5 eq)	0 °C	1 h	<25%
5	NHMDS (1.5 eq)	−40 °C	1 h	<10%
6	NHMDS (1.5 eq)	−78 °C	1 h	<33%
7	LHMDS (1.5 eq)	−78 °C	1 h	<30%
8	KHMDS (1.5 eq)	−78 °C	1 h	<38%
9	LDA (1.5 eq)	0 °C	1 h	<12%
10	LDA (1.5 eq)	−40 °C	1 h	93% (isolated yield)
11	LDA (1.5 eq)	−78 °C	1 h	90% (isolated yield)
12[b]	LDA (1.5 eq)	−78 °C→rt	3 h	<33%

a) Measured by ^{1}H-NMR. *b*) Selectfluor (1.2 eq) in MeCN was used.

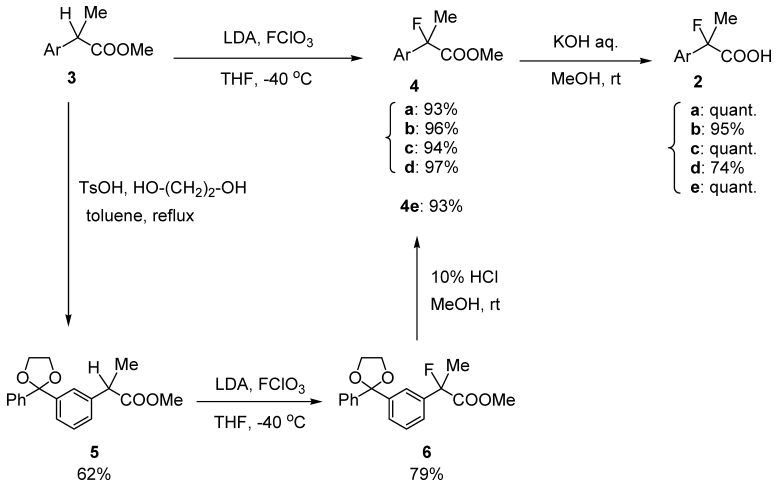


Chart 2

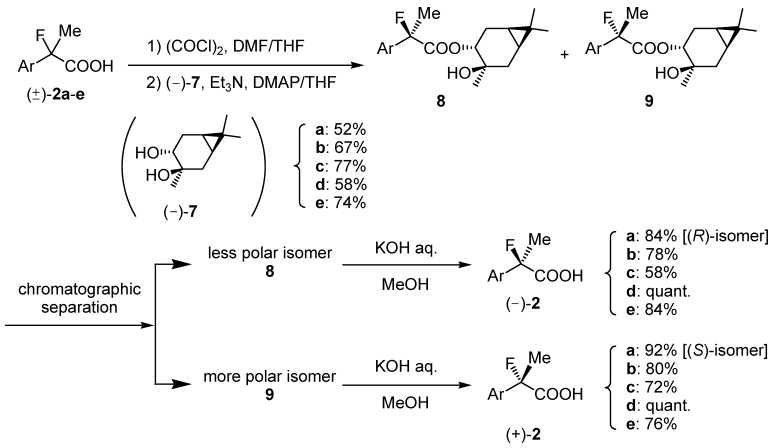


Chart 3

the optically active 2-aryl-2-fluoropropionic acids by electrophilic fluorination of racemic 2-arylpropionic acid esters with $FClO_3$ followed by optical resolution *via* the (−)-carenediol ester diastereomers. Absolute configurations were determined by X-ray crystallographic analyses. In order to clarify both the effects of the fluorine introduction and the effects derived from the stereochemical difference, biological assays of each enantiomer of these fluorinated acids are currently underway.

Experimental

Melting points were measured with a Yanaco micro melting point apparatus and uncorrected. Spectroscopic measurements were carried out with the following instruments: optical rotations, JASCO DIP-1000 digital polarimeter; IR spectra, JASCO FT/IR-460 Plus; mass spectra (MS), JEOL JMS-GCmate; high resolution mass spectra (HR-MS), JEOL JMS-AX 505 HAD; ^{1}H-NMR spectra, JEOL JNM-GX 270 (270 MHz) in $CDCl_3$ or CD_3OD with TMS (=0.00 ppm) as an internal standard; ^{19}F-NMR spectra, JEOL JNM-GX 270 (254 MHz), in $CDCl_3$ or CD_3OD with $CFCl_3$ (=0.00 ppm) as an internal standard. Open column chromatography, flash column chromatography, and thin layer chromatography were performed on silica gel [Merck silica gel 60 (0.040—0.063 mm), Kanto chemical silica gel 60N (0.040—0.050 mm) and Merck 5715, respectively].

General Procedure for Preparation of Methyl 2-Arylpropionates 3a—e Thionyl chloride (8.0 mmol) was added to a stirred solution of commercially available 2-arylpropionic acid **1** (4.0 mmol) in dry MeOH (30 ml) at 0 °C. Stirring was continued at room temperature for 1—2 h. Saturated aqueous $NaHCO_3$ (15 ml) was added to the reaction mixture, the MeOH was evaporated, and the resulting mixture was extracted with AcOEt (30 ml×3). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residual oil was purified by column chromatography on silica gel (hexane/AcOEt=4/1), or by recrystallization from hexane/AcOEt to give methyl esters **3a**—**e** in 95—100% yields.

Methyl 2-[4-(2-Methylpropyl)phenyl]propionate [(±)-**3a**]: Colorless oil. IR (neat) cm^{-1}: 1740 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.49 (3H, d, J=7 Hz), 1.82 (1H, sep, J=7 Hz), 2.44 (2H, d, J=7 Hz), 3.67 (3H, s), 3.70 (1H, q, J=7 Hz), 7.09 (2H, d, J=8 Hz), 7.20 (2H, d, J=8 Hz). MS m/z: 220 (M^+), 161. HR-MS Calcd for $C_{14}H_{20}O_2$ (M^+): 220.1463. Found: 220.1465.

Methyl 2-[6-Methoxy(2-naphthyl)]propionate [(±)-**3b**]: Colorless prisms (from hexane/AcOEt). mp 85—87 °C. IR (KBr) cm^{-1}: 1740 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.57 (3H, d, J=7 Hz), 3.66 (3H, s), 3.85 (1H, q, J=7 Hz), 3.89 (3H, s), 7.10—7.15 (2H, m), 7.39 (1H, dd, J=2, 8 Hz), 7.65 (1H, d, J=2 Hz), 7.68 (1H, s), 7.71 (1H, s). MS m/z: 244 (M^+), 185. HR-MS Calcd for $C_{15}H_{16}O_3$ (M^+): 244.1099. Found: 244.1053.

Methyl 2-(3-Fluoro-4-phenylphenyl)propionate [(±)-**3c**]: Colorless oil. IR (neat) cm^{-1}: 1738 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, d, J=7 Hz), 3.70 (3H, s), 3.76 (1H, q, J=7 Hz), 7.09—7.16 (2H, m), 7.33—7.46 (4H, m), 7.51—7.55 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −118.13 (1F, t, J=10 Hz). MS m/z: 258 (M^+), 199. HR-MS Calcd for $C_{16}H_{15}FO_2$ (M^+): 258.1056. Found: 258.1080.

Methyl 2-(4-Phenoxyphenyl)propionate [(±)-**3d**]: Colorless oil. IR (neat) cm^{-1}: 1739 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, d, J=7 Hz), 3.66 (3H, s), 3.70 (1H, q, J=7 Hz), 6.85—6.89 (1H, m), 6.97—7.13 (5H, m), 7.24—7.37 (3H, m). MS m/z: 256 (M^+), 197, 179. HR-MS Calcd for $C_{16}H_{16}O_3$ (M^+): 256.1099. Found: 256.1074.

Methyl 2-[3-(Phenylcarbonyl)phenyl]propionate [(±)-**3e**]: Colorless oil. IR (neat) cm^{-1}: 1660 (C=O), 1738 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, d, J=7 Hz), 3.68 (3H, s), 3.81 (1H, q, J=7 Hz), 7.41—7.83 (9H, m). MS m/z: 268 (M^+), 209, 191. HR-MS Calcd for $C_{17}H_{16}O_3$ (M^+): 268.1099. Found: 268.1097.

Preparation of Methyl 2-[3-(2-Phenyl-1,3-dioxolan-2-yl)phenyl]propionate [(±)-5] A mixture of methyl ester **3e** (1.0 g, 3.7 mmol), ethylene glycol (0.85 ml, 15 mmol), *p*-toluenesulfonic acid monohydrate (70 mg, 0.37 mmol), and toluene (20 ml) was heated at reflux for 18 h. Saturated aqueous $NaHCO_3$ (10 ml) was added to the reaction mixture and the whole was extracted with AcOEt (30 ml×3). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residual oil was purified by column chromatography on silica gel (hexane/AcOEt=4/1) to give **5** as an oil in 62% yield. Colorless oil. IR (neat) cm^{-1}: 1737 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, d, J=7 Hz), 3.63 (3H, s), 3.71 (1H, q, J=7 Hz), 4.05 (4H, s), 7.21—7.39 (6H, m), 7.45—7.52 (3H, m). MS m/z: 312 (M^+), 268, 253, 235. HR-MS Calcd for $C_{19}H_{20}O_4$ (M^+): 312.1362. Found: 312.1364.

General Procedure for Preparation of Methyl 2-Aryl-2-fluoropropionates 4a—d and 6 A solution of methyl esters **3** or **5** (4.0 mmol) in dry THF (5 ml) was added to a stirred solution of lithium diisopropylamide [1.5 eq, prepared at 0 °C from diisopropylamine and butyllithium (1.5 M in hexane) in dry THF (15 ml)] cooled at −40 °C. The stirred solution was maintained at −40 °C for 10 min and diluted $FClO_3$ gas in nitrogen[9—11] was introduced for 1 h. Hexane (10 ml) was added and the resulting mixture was filtered through a short column chromatography on silica gel to remove polar substances. After the solvent was evaporated, the residual oil was purified by column chromatography on silica gel (hexane/AcOEt=4/1) or by recrystallization from hexane/AcOEt to give 2-fluorinated esters **4** or **6** in 79—97% yields.

Methyl 2-Fluoro-2-[4-(2-methylpropyl)phenyl]propionate [(±)-**4a**]: Colorless oil. IR (neat) cm^{-1}: 1743 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.81—1.91 (1H, m), 1.93 (3H, d, J=22 Hz), 2.47 (2H, d, J=7 Hz), 3.77 (3H, s), 7.16 (2H, d, J=8 Hz), 7.39 (2H, d, J=8 Hz). ^{19}F-NMR ($CDCl_3$) δ: −150.83 (1F, q, J=22 Hz). MS m/z: 238 (M^+), 218, 179. HR-MS Calcd for $C_{14}H_{19}FO_2$ (M^+): 238.1369. Found: 238.1370.

Methyl 2-Fluoro-2-[6-methoxy(2-naphthyl)]propionate [(±)-**4b**]: Colorless solid (from hexane/AcOEt). mp 94—96 °C. IR (KBr) cm^{-1}: 1743 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, d, J=22 Hz), 3.77 (3H, s), 3.92 (3H, s), 7.13 (1H, d, J=2 Hz), 7.17 (1H, dd, J=2, 9 Hz), 7.55 (1H, dd, J=2, 9 Hz), 7.74 (1H, s), 7.77 (1H, d, J=1 Hz), 7.89 (1H, d, J=1 Hz). ^{19}F-NMR ($CDCl_3$) δ: −150.77 (1F, q, J=22 Hz). MS m/z: 262 (M^+), 242, 203. HR-MS Calcd for $C_{15}H_{15}FO_3$ (M^+): 262.1005. Found: 262.0959.

Methyl 2-Fluoro-2-(3-fluoro-4-phenylphenyl)propionate [(±)-**4c**]: Colorless needles (from hexane/$CHCl_3$). mp 67—70 °C. IR (KBr) cm^{-1}: 1748 (C=O). ^{1}H-NMR (CD_3OD) δ: 1.96 (3H, dd, J=2, 22 Hz), 3.81 (3H, s), 7.30—7.56 (8H, m). ^{19}F-NMR (CD_3OD) δ: −117.26—−117.94 (1F, m), −152.38 (1F, q, J=22 Hz). MS m/z: 276 (M^+), 217. HR-MS Calcd for $C_{16}H_{14}F_2O_2$ (M^+): 276.0962. Found: 276.0962.

Methyl 2-Fluoro-2-(4-phenoxyphenyl)propionate [(±)-**4d**]: Yellow oil. IR (neat) cm^{-1}: 1744 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.91 (3H, d, J=22 Hz), 3.77 (3H, s), 6.93—7.03 (3H, m), 7.09—7.26 (3H, m), 7.30—7.38 (3H, m). ^{19}F-NMR ($CDCl_3$) δ: −151.85 (1F, q, J=22 Hz). MS *m/z*: 274 (M^+), 255, 215. HR-MS Calcd for $C_{16}H_{15}FO_3$ (M^+): 274.1006. Found: 274.0977.

Methyl 2-Fluoro-2-[3-(2-phenyl-1,3-dioxolan-2-yl)phenyl]propionate [(±)-**6**]: Colorless oil. IR (neat) cm^{-1}: 1742 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.91 (3H, d, J=22 Hz), 3.74 (3H, s), 4.06 (4H, s), 7.24—7.37 (4H, m), 7.40—7.52 (4H, m), 7.71 (1H, t, J=2Hz). ^{19}F-NMR ($CDCl_3$) δ: −151.85 (1F, q, J=22 Hz). MS *m/z*: 330 (M^+), 271. HR-MS Calcd for $C_{19}H_{19}FO_4$ (M^+): 330.1267. Found: 330.1265.

Preparation of Methyl 2-Fluoro-2-[3-(phenylcarbonyl)phenyl]propionate [(±)-4e] Ten percent aqueous HCl (5 ml) was added to a solution of 2-fluorinated ester **6** (562 mg, 1.7 mmol) in MeOH (5 ml) and the mixture was stirred at room temperature for 18 h. Saturated aqueous $NaHCO_3$ was added to the reaction mixture, the MeOH was evaporated and the aqueous layer was extracted with AcOEt (20 ml×3). The organic layer was washed with brine and dried over Na_2SO_4. After the solvent was evaporated, the residual oil was purified by column chromatography on silica gel (hexane/AcOEt=4/1) to give 2-fluorinated ester **4e** in 93% yield. Colorless oil. IR (neat) cm^{-1}: 1661 (C=O), 1744 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.97 (3H, d, J=22 Hz), 3.78 (3H, s), 7.46—7.66 (4H, m), 7.73—7.81 (4H, m), 7.96 (1H, d, J=2 Hz). ^{19}F-NMR ($CDCl_3$) δ: −152.43 (1F, q, J=22 Hz). MS *m/z*: 330 (M^+), 271. HR-MS Calcd for $C_{19}H_{19}FO_4$ (M^+): 330.1267. Found: 330.1265.

General Procedure for Preparation of 2-Aryl-2-fluoropropionic Acids 2a—e 1 M KOH (3 ml) was added to a solution of 2-fluorinated esters **4** (2.0 mmol) in MeOH (5 ml) and the mixture was stirred at room temperature for 1—3 h. After evaporation of MeOH, the aqueous layer was washed with ether (10 ml×2), acidified with 10% HCl (pH 1) and extracted with CH_2Cl_2 (20 ml×3). The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave 2-aryl-2-fluoropropionic acids (±)-**2a**—**e** in 74—100% yields.

2-Fluoro-2-[4-(2-methylpropyl)phenyl]propionic Acid [(±)-**2a**]: Colorless solid (from hexane/AcOEt). mp 68—70 °C. IR (KBr) cm^{-1}: 1715 (C=O), 3438 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (6H, d, J=7 Hz), 1.83—1.91 (1H, m), 1.87 (3H, d, J=22 Hz), 2.47 (2H, d, J=7 Hz), 7.14 (2H, d, J=8 Hz), 7.38 (2H, d, J=8 Hz). ^{19}F-NMR ($CDCl_3$) δ: −149.46 (1F, q, J=22 Hz). MS *m/z*: 224 (M^+), 179. HR-MS Calcd for $C_{13}H_{17}FO_2$ (M^+): 224.1213. Found: 224.1180.

2-Fluoro-2-[6-methoxy(2-naphthyl)]propionic Acid [(±)-**2b**]: Colorless prisms (from hexane/AcOEt). mp 119—122 °C. IR (KBr) cm^{-1}: 1739 (C=O), 3445 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, d, J=22 Hz), 3.91 (3H, s), 7.11—7.18 (2H, m), 7.57 (1H, dd, J=2, 9 Hz), 7.73 (1H, s), 7.76 (1H, s), 7.92 (1H, d, J=1 Hz). ^{19}F-NMR ($CDCl_3$) δ: −150.16 (1F, q, J=22 Hz). MS *m/z*: 248 (M^+), 203. HR-MS Calcd for $C_{14}H_{13}FO_3$ (M^+): 248.0849. Found: 248.0837.

2-Fluoro-2-(3-fluoro-4-phenylphenyl)propionic Acid [(±)-**2c**]: Colorless solid (from hexane/MeOH). mp 97—100 °C. IR (KBr) cm^{-1}: 1618 (C=O), 3406 (OH). ^{1}H-NMR (CD_3OD) δ: 1.86 (3H, d, J=22 Hz), 7.32—7.44 (6H, m), 7.47—7.54 (2H, m). ^{19}F-NMR (CD_3OD) δ: −118.71—−118.78 (1F, m), −141.55 (1F, q, J=22 Hz). MS *m/z*: 262 (M^+), 217. HR-MS Calcd for $C_{15}H_{12}F_2O_2$ (M^+): 262.0805. Found: 262.0798.

2-Fluoro-2-(4-phenoxyphenyl)propionic Acid [(±)-**2d**]: Colorless solid (from hexane/AcOEt). mp 62—66 °C. IR (KBr) cm^{-1}: 1725 (C=O), 3074 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.92 (3H, d, J=23 Hz), 6.70—7.37 (9H, m). ^{19}F-NMR ($CDCl_3$) δ: −151.70 (1F, q, J=23 Hz). MS *m/z*: 260 (M^+), 240, 215. HR-MS Calcd for $C_{15}H_{13}FO_3$ (M^+): 260.0849. Found: 260.0848.

2-Fluoro-2-[3-(phenylcarbonyl)phenyl]propionic Acid [(±)-**2e**]: Yellow oil. IR (neat) cm^{-1}: 1660 (C=O), 1738 (C=O), 3066 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, d, J=22 Hz), 7.45—7.64 (4H, m), 7.76—7.81 (4H, m), 7.99 (1H, t, J=2 Hz). ^{19}F-NMR ($CDCl_3$) δ: −152.50 (1F, q, J=22 Hz). MS *m/z*: 272 (M^+), 227. HR-MS Calcd for $C_{16}H_{13}FO_3$ (M^+): 272.0849. Found: 272.0823.

General Procedure of Preparation of (1*R*,2*R*,3*R*,6*S*)-4-Hydroxy-4,7,7-trimethyl-bicyclo[4.1.0]hept-3-yl 2-Aryl-2-fluoropropionates 8a—e and 9a—e $(COCl)_2$ (8.0 mmol) was added to a solution of 2-aryl-2-fluoropropionic acids **2** (4.0 mmol) and *N*,*N*-dimethylformamide (DMF, 0.4 mmol) in dry THF (30 ml) at 0 °C and the mixture was stirred at room temperature for 2—5 h. After evaporation of the excess reagents and solvent, the residual oil was dried well under vacuum. Then the crude product was solved in dry THF (30 ml) and *N*,*N*-dimethylaminopyridine (DMAP, 0.4 mmol) and chiral alcohol **7** (4.0 mmol) were added to this solution. Et_3N (8.0 mmol) was then added slowly to the reaction, and the mixture was stirred at room temperature for 2—5 h. Hexane was then added and the resulting mixture was filtered through a chromatographic column of silica gel to remove polar substances. Evaporation of solvent gave the mixture of the diastereomers **8** and **9**. These were separated by column chromatography on silica gel (hexane/AcOEt=4/1 or $CHCl_3$/AcOEt=95/5) to give the ester diastereomers **8a**—**e** and **9a**—**e**, respectively (the yields of each pair of the ester diastereomers were 52—77% in 2 steps).

(1*R*,2*R*,3*R*,6*S*)-4-Hydroxy-4,7,7-trimethyl-bicyclo[4.1.0]hept-3-yl (2*R*)-2-Fluoro-2-[4-(2-methylpropyl)phenyl]propionate (**8a**): Colorless oil. IR (neat) cm^{-1}: 1739 (C=O), 3456 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.64—0.76 (2H, m), 0.89 (6H, d, J=7 Hz), 0.97 (3H, s), 1.00 (3H, s), 1.16 (3H, s), 1.20—1.31 (1H, m), 1.58—1.70 (1H, m), 1.80—1.96 (2H, m), 1.94 (3H, d, J=22 Hz), 2.15 (1H, dd, J=8, 15 Hz), 2.47 (2H, d, J=7 Hz), 4.55 (1H, dd, J=8, 10 Hz), 7.16 (2H, d, J=8 Hz), 7.40 (2H, d, J=8 Hz). ^{19}F-NMR ($CDCl_3$) δ: −148.96 (1F, q, J=22 Hz). MS *m/z*: 376 (M^+), 358. HR-MS Calcd for $C_{23}H_{33}FO_3$ (M^+): 376.2414. Found: 376.2420.

(1*R*,2*R*,3*R*,6*S*)-4-Hydroxy-4,7,7-trimethyl-bicyclo[4.1.0]hept-3-yl (2*S*)-2-Fluoro-2-[4-(2-methylpropyl)phenyl]propionate (**9a**): Colorless oil. IR (neat) cm^{-1}: 1733 (C=O), 3436 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.65—0.77 (2H, m), 0.89 (6H, d, J=7 Hz), 0.93 (3H, s), 0.96 (3H, s), 1.16—1.33 (1H, m), 1.20 (3H, s), 1.63—1.75 (1H, m), 1.82—2.01 (2H, m), 1.92 (3H, d, J=22 Hz), 2.11 (1H, dd, J=8, 15 Hz), 2.47 (2H, d, J=7 Hz), 4.58 (1H, dd, J=8, 10 Hz), 7.15 (2H, d, J=8 Hz), 7.38 (2H, d, J=8 Hz). ^{19}F-NMR ($CDCl_3$) δ: −151.47 (1F, q, J=22 Hz). MS *m/z*: 376 (M^+), 358. HR-MS Calcd for $C_{23}H_{33}FO_3$ (M^+): 376.2414. Found: 376.2401.

(1*R*,2*R*,3*R*,6*S*)-4-Hydroxy-4,7,7-trimethyl-bicyclo[4.1.0]hept-3-yl (2*R*)-2-Fluoro-2-[6-methoxy(2-naphthyl)]propionate (**8b**): Colorless oil. IR (neat) cm^{-1}: 1739 (C=O), 3511 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.63—0.75 (2H, m), 0.96 (3H, s), 0.99 (3H, s), 1.17 (3H, s), 1.23—1.32 (1H, m), 1.58—1.69 (1H, m), 1.90—1.99 (1H, m), 2.03 (3H, d, J=22 Hz), 2.15 (1H, dd, J=8, 15 Hz), 3.92 (3H, s), 4.58 (1H, dd, J=7, 10 Hz), 7.12 (1H, d, J=2 Hz), 7.17 (1H, dd, J=2, 9 Hz), 7.52 (1H, dd, J=2, 9 Hz), 7.74 (1H, s), 7.77 (1H, s), 7.90 (1H, d, J=1 Hz). ^{19}F-NMR ($CDCl_3$) δ: −149.20 (1F, q, J=22 Hz). MS *m/z*: 400 (M^+). HR-MS Calcd for $C_{24}H_{29}FO_4$ (M^+): 400.2050. Found: 400.2066.

(1*R*,2*R*,3*R*,6*S*)-4-Hydroxy-4,7,7-trimethyl-bicyclo[4.1.0]hept-3-yl (2*S*)-2-Fluoro-2-[6-methoxy(2-naphthyl)]propionate (**9b**): Colorless prisms (from hexane/$CHCl_3$). mp 111—116 °C. IR (KBr) cm^{-1}: 1745 (C=O), 3506 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.63—0.77 (2H, m), 0.96 (3H, s), 0.98 (3H, s), 1.20 (3H, s), 1.26—1.32 (1H, m), 1.62—1.74 (1H, m), 1.92—2.01 (1H, m), 2.02 (3H, d, J=22 Hz), 2.04—2.14 (1H, m), 3.93 (3H, s), 4.61 (1H, dd, J=8, 10 Hz), 7.12 (1H, d, J=2 Hz), 7.17 (1H, dd, J=2, 9 Hz), 7.54 (1H, dd, J=2, 9 Hz), 7.73 (1H, s), 7.76 (1H, s), 7.89 (1H, d, J=2 Hz). ^{19}F-NMR ($CDCl_3$) δ: −150.62 (1F, q, J=22 Hz). MS *m/z*: 400 (M^+). HR-MS Calcd for $C_{24}H_{29}FO_4$ (M^+): 400.2050. Found: 400.2064.

Crystal Data: $C_{24}H_{29}O_4F$, M=400.49, orthorhombic, $P2_12_12_1$ (no 19), a=6.444 (2), b=14.743 (6), c=22.452 (8) Å, V=2132.9 (13) Å^3, Z=4, D_C=1.291 g/cm^3, μ(Mo$K\alpha$)=0.93 cm^{-1}, T=173 K, colorless prism (0.30×0.20×0.20 mm), 31168 measured, 4881 unique, R_1=0.032, wR_2=0.075 for all reflections (SIR 92 refinement).

(1*R*,2*R*,3*R*,6*S*)-4-Hydroxy-4,7,7-trimethyl-bicyclo[4.1.0]hept-3-yl (2*R*)-2-Fluoro-2-(3-fluoro-4-phenylphenyl)propionate (**8c**): Colorless prisms (from hexane/AcOEt). mp 61—65 °C. IR (KBr) cm^{-1}: 1732 (C=O), 3444 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.67—0.79 (2H, m), 1.01 (3H, s), 1.03 (3H, s), 1.16—1.37 (1H, m), 1.25 (3H, s), 1.58—1.75 (1H, m), 1.86—2.05 (1H, m), 1.96 (3H, d, J=22 Hz), 2.16 (1H, dd, J=8, 14 Hz), 4.61 (1H, dd, J=8, 10 Hz), 7.31—7.56 (8H, m). ^{19}F-NMR ($CDCl_3$) δ: −117.19—−117.27 (1F, m), −151.22 (1F, q, J=22 Hz). MS *m/z*: 414 (M^+), 396. HR-MS Calcd for $C_{25}H_{28}F_2O_3$ (M^+): 414.2007. Found: 414.1987.

Crystal Data: $C_{25}H_{28}O_3F_2$, M=414.49, monoclinic, $C2$ (no 5), a=32.445 (9), b=5.939 (2), c=25.451 (8) Å, β=100.3712 (9)°, V=4824.0 (24) Å^3, Z=8, D_C=1.141 g/cm^3, μ(Mo$K\alpha$)=0.84 cm^{-1}, T=173 K, colorless prism (0.20×0.20×0.20 mm), 35780 measured, 10916 unique, R_1=0.075, wR_2=0.083 for all reflections (SIR 92 refinement).

(1*R*,2*R*,3*R*,6*S*)-4-Hydroxy-4,7,7-trimethyl-bicyclo[4.1.0]hept-3-yl (2*S*)-2-Fluoro-2-(3-fluoro-4-phenylphenyl)propionate (**9c**): Colorless oil. IR (neat) cm^{-1}: 1741 (C=O), 3465 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.67—0.78 (2H, m), 0.98 (3H, s), 1.01 (3H, s), 1.15—1.37 (1H, m), 1.25 (3H, s), 1.64—1.80 (1H, m), 1.88—2.05 (1H, m), 1.96 (3H, d, J=22 Hz), 2.14 (1H, dd, J=7, 14 Hz), 4.64 (1H, dd, J=7, 10 Hz), 7.30—7.56 (8H, m). ^{19}F-NMR ($CDCl_3$) δ: −117.20—−117.28 (1F, m), −151.83 (1F, q, J=22 Hz). MS *m/z*: 414 (M^+), 396. HR-MS Calcd for $C_{25}H_{28}F_2O_3$ (M^+): 414.2007. Found: 414.1991.

(1*R*,2*R*,3*R*,6*S*)-4-Hydroxy-4,7,7-trimethyl-bicyclo[4.1.0]hept-3-yl (2*R*)-2-

Fluoro-2-(4-phenoxyphenyl)propionate (**8d**): Colorless oil. IR (neat) cm^{-1}: 1739 (C=O), 3453 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.68—0.74 (2H, m), 0.98 (3H, s), 1.00 (3H, s), 1.11—1.33 (1H, m), 1.18 (3H, s), 1.55—1.67 (1H, m), 1.75—2.00 (1H, m), 1.91 (3H, d, J=22 Hz), 2.13 (1H, dd, J=7, 14 Hz), 4.56 (1H, dd, J=8, 10 Hz), 6.94—7.10 (3H, m), 7.11—7.24 (3H, m), 7.26—7.37 (3H, m). ^{19}F-NMR ($CDCl_3$) δ: −150.33 (1F, q, J=22 Hz). MS m/z: 412 (M^+), 394. HR-MS Calcd for $C_{25}H_{29}FO_4$ (M^+): 412.2050. Found: 412.2079.

(1*R*,2*R*,3*R*,6*S*)-4-Hydroxy-4,7,7-trimethyl-bicyclo[4.1.0]hept-3-yl (2*S*)-2-Fluoro-2-(4-phenoxyphenyl)propionate (**9d**): Colorless oil. IR (neat) cm^{-1}: 1741 (C=O), 3495 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.68—0.74 (2H, m), 0.97 (3H, s), 0.99 (3H, s), 1.18—1.35 (1H, m), 1.19 (3H, s), 1.47—1.73 (1H, m), 1.85—1.98 (1H, m), 1.90 (3H, d, J=22 Hz), 2.08 (1H, dd, J=8, 14 Hz), 4.59 (1H, dd, J=8, 10 Hz), 6.94—7.02 (3H, m), 7.09—7.23 (3H, m), 7.31—7.37 (3H, m). ^{19}F-NMR ($CDCl_3$) δ: −150.90 (1F, q, J=22 Hz). MS m/z: 412 (M^+), 394. HR-MS Calcd for $C_{25}H_{29}FO_4$ (M^+): 412.2050. Found: 412.2079.

(1*R*,2*R*,3*R*,6*S*)-4-Hydroxy-4,7,7-trimethyl-bicyclo[4.1.0]hept-3-yl (2*R*)-2-Fluoro-2-[3-(phenylcarbonyl)phenyl]propionate (**8e**): Colorless prisms (from hexane/$CHCl_3$). mp 87—90 °C. IR (KBr) cm^{-1}: 1645 (C=O), 1758 (C=O), 3504 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.70—0.75 (2H, m), 0.98 (3H, s), 1.00 (3H, s), 1.18—1.35 (1H, m), 1.25 (3H, s), 1.61—1.78 (1H, m), 1.90—2.05 (1H, m), 1.98 (3H, d, J=22 Hz), 2.18 (1H, dd, J=8, 10 Hz), 4.59 (1H, dd, J=8, 10 Hz), 7.47—7.53 (3H, m), 7.58—7.64 (1H, m), 7.73—7.82 (4H, m), 8.01 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −151.85 (1F, q, J=22 Hz). MS m/z: 424 (M^+), 406. HR-MS Calcd for $C_{26}H_{29}FO_4$ (M^+): 424.2050. Found: 424.2074.

Crystal Data: $C_{29}H_{29}O_4F$, M=460.54, orthorhombic, $P2_12_12_1$ (no 19), a=11.193 (4), b=11.949 (4), c=16.874 (6), V=2256.8 (14) Å^3, Z=4, D_C=1.355 g/cm^3, μ(Mo$K\alpha$)=0.94 cm^{-1}, T=173 K, colorless prism (0.20×0.20×0.20 mm), 29955 measured, 5095 unique, R_1=0.041, wR_2=0.075 for all reflections (SIR 97 refinement).

(1*R*,2*R*,3*R*,6*S*)-4-Hydroxy-4,7,7-trimethyl-bicyclo[4.1.0]hept-3-yl (2*S*)-2-Fluoro-2-[3-(phenylcarbonyl)phenyl]propionate (**9e**): Colorless oil. IR (neat) cm^{-1}: 1661 (C=O), 1752 (C=O), 3500 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.70—0.75 (2H, m), 0.98 (3H, s), 0.99 (3H, s), 1.20—1.34 (1H, m), 1.23 (3H, s), 1.56—1.76 (1H, m), 1.90—2.05 (1H, m), 1.97 (3H, d, J=22 Hz), 2.10 (1H, dd, J=8, 15 Hz), 4.62 (1H, dd, J=8, 10 Hz), 7.46—7.53 (3H, m), 7.58—7.62 (1H, m), 7.72—7.81 (4H, m), 7.98 (1H, t, J=2 Hz). ^{19}F-NMR ($CDCl_3$) δ: −151.81 (1F, q, J=22 Hz). MS m/z: 424 (M^+), 406. HR-MS Calcd for $C_{26}H_{29}FO_4$ (M^+): 424.2050. Found: 424.2080.

Preparation of Chiral 2-Aryl-2-fluoropropionic Acids 2a—e by Hydrolysis of Esters 8 or 9 1 M KOH (1.5 ml) was added to a solution of esters of **8** or **9** (1.0 mmol) in MeOH (5 ml) was added to and the mixture was stirred at room temperature for 1—2 h. After evaporation of MeOH at room temperature, the aqueous layer was washed with ether (10 ml×3), acidified with 10% HCl (pH 1) and extracted with CH_2Cl_2 (20 ml×3). The organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residual oil was purified by column chromatography on silica gel (AcOEt or MeOH/acetone=1/9) gave chiral 2-aryl-2-propionic acids **2a**—**e** in 58—100% yields.

In the case of hydrolysis of esters **8c** and **9c**, washing with either was omitted, because **2c** is insoluble in alkaline solutions.

(*R*)-(−)-**2a**: Colorless solid (from hexane/AcOEt). mp 164—165 °C. $[\alpha]_D^{27}$ −27.1° (c=1.1, EtOH). IR (KBr) cm^{-1}: 1716 (C=O), 3421 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (6H, d, J=7 Hz), 1.87 (3H, d, J=22 Hz), 1.83—1.91 (1H, m), 2.47 (2H, d, J=7 Hz), 7.14 (2H, d, J=8 Hz), 7.38 (2H, d, J=8 Hz). ^{19}F-NMR ($CDCl_3$) δ: −149.46 (1F, q, J=22 Hz). MS m/z: 224 (M^+), 179. HR-MS Calcd for $C_{13}H_{17}FO_2$ (M^+): 224.1213. Found: 224.1201.

(*S*)-(+)-**2a**: Colorless solid (from hexane/AcOEt). mp 159—163 °C. $[\alpha]_D^{25}$ +30.6° (c=1.0, EtOH). IR (KBr) cm^{-1}: 1716 (C=O), 3419 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (6H, d, J=7 Hz), 1.87 (3H, d, J=22 Hz), 1.83—1.91 (1H, m), 2.47 (2H, d, J=7 Hz), 7.14 (2H, d, J=8 Hz), 7.38 (2H, d, J=8 Hz). ^{19}F-NMR ($CDCl_3$) δ: −149.46 (1F, q, J=22 Hz). MS m/z: 224 (M^+), 179. HR-MS Calcd for $C_{13}H_{17}FO_2$ (M^+): 224.1213. Found: 224.1222.

(*R*)-(−)-**2b**: Colorless prisms (from hexane/AcOEt). mp 113—115 °C. $[\alpha]_D^{26}$ −46.9° (c=1.0, MeOH). IR (KBr) cm^{-1}: 1739 (C=O), 3442 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, d, J=22 Hz), 3.91 (3H, s), 7.11—7.18 (2H, m), 7.57 (1H, dd, J=2, 9 Hz), 7.73 (1H, s), 7.76 (1H, s), 7.92 (1H, d, J=1 Hz). ^{19}F-NMR ($CDCl_3$) δ: −150.16 (1F, q, J=22 Hz). MS m/z: 248 (M^+), 203. HR-MS Calcd for $C_{14}H_{13}FO_3$ (M^+): 248.0849. Found: 248.0837.

(*S*)-(+)-**2b**: Colorless prisms (from hexane/AcOEt). mp 112—115 °C. $[\alpha]_D^{26}$ +46.5° (c=1.0, MeOH). IR (KBr) cm^{-1}: 1737 (C=O), 3447 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, d, J=22 Hz), 3.91 (3H, s), 7.11—7.18 (2H, m), 7.57 (1H, dd, J=2, 9 Hz), 7.73 (1H, s), 7.76 (1H, s), 7.92 (1H, d, J=1 Hz). ^{19}F-NMR ($CDCl_3$) δ: −150.16 (1F, q, J=22 Hz). MS m/z: 248 (M^+), 203. HR-MS Calcd for $C_{14}H_{13}FO_3$ (M^+): 248.0849. Found: 248.0871.

(*R*)-(−)-**2c**: Colorless solid (from hexane/MeOH). mp 111—113 °C. $[\alpha]_D^{25}$ −33.8° (c=1.0, MeOH). IR (KBr) cm^{-1}: 1619 (C=O), 3423 (OH). ^{1}H-NMR (CD_3OD) δ: 1.86 (3H, d, J=22 Hz) 7.32—7.44 (6H, m), 7.47—7.54 (2H, m). ^{19}F-NMR (CD_3OD) δ: −118.71—−118.78 (1F, m), −141.55 (1F, q, J=22 Hz). MS m/z: 262 (M^+), 242, 217. HR-MS Calcd for $C_{15}H_{12}F_2O_2$ (M^+): 262.0805. Found: 262.0784.

(*S*)-(+)-**2c**: Colorless solid (from hexane/MeOH). mp 112—115 °C. $[\alpha]_D^{26}$ +33.9° (c=1.0, MeOH). IR (KBr) cm^{-1}: 1619 (C=O), 3410 (OH). ^{1}H-NMR (CD_3OD) δ: 1.86 (3H, d, J=22 Hz), 7.32—7.44 (6H, m), 7.47—7.54 (2H, m). ^{19}F-NMR (CD_3OD) δ: −118.71—−118.78 (1F, m), −141.55 (1F, q, J=22 Hz). MS m/z: 262 (M^+), 242, 217. HR-MS Calcd for $C_{15}H_{12}F_2O_2$ (M^+): 262.0805. Found: 262.0789.

(*R*)-(−)-**2d**: Yellow oil. $[\alpha]_D^{25}$ −3.1° (c=1.2, $CHCl_3$). IR (neat) cm^{-1}: 1729 (C=O), 2990 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.92 (3H, d, J=23 Hz), 6.70—7.37 (9H, m). ^{19}F-NMR ($CDCl_3$) δ: −151.70 (1F, q, J=23 Hz). MS m/z: 260 (M^+), 215. HR-MS Calcd for $C_{15}H_{13}FO_3$ (M^+): 260.0849. Found: 260.0846.

Crystal Data for (*S*)-(−)-Phenethylamine Salt of (−)-**2d**: $C_{23}H_{24}NO_3F$, M=381.45, orthorhombic, $P2_12_12_1$ (no 19), a=6.646 (2), b=14.101 (5), c=21.855 (7), V=2048.0 (11) Å^3, Z=4, D_C=1.237 g/cm^3, μ(Mo$K\alpha$)=0.87 cm^{-1}, T=173 K, colorless prism (0.30×0.05×0.05 mm), 17373 measured, 4491 unique, R_1=0.053, wR_2=0.142 for all reflections (SIR 97 refinement).

(*S*)-(+)-**2d**: Yellow oil. $[\alpha]_D^{26}$ +3.2° (c=1.4, $CHCl_3$). IR (neat) cm^{-1}: 1731 (C=O), 2989 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.92 (3H, d, J=23 Hz), 6.70—7.37 (9H, m). ^{19}F-NMR ($CDCl_3$) δ: −151.70 (1F, q, J=23 Hz). MS m/z: 260 (M^+), 215. HR-MS Calcd for $C_{15}H_{13}FO_3$ (M^+): 260.0849. Found: 260.0884.

(*R*)-(−)-**2e**: Yellow oil. $[\alpha]_D^{25}$ −4.9° (c=0.9, $CHCl_3$). IR (neat) cm^{-1}: 1660 (C=O), 1740 (C=O), 2990 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, d, J=22 Hz), 7.45—7.64 (4H, m), 7.76—7.81 (4H, m), 7.99 (1H, t, J=2 Hz). ^{19}F-NMR ($CDCl_3$) δ: −152.50 (1F, q, J=22 Hz). MS m/z: 272 (M^+), 227. HR-MS Calcd for $C_{16}H_{13}FO_3$ (M^+): 272.0849. Found: 272.0825.

(*S*)-(+)-**2e**: Yellow oil. $[\alpha]_D^{28}$ +4.9° (c=0.7, $CHCl_3$). IR (neat) cm^{-1}: 1660 (C=O), 1734 (C=O), 3066 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, d, J=22 Hz), 7.45—7.64 (4H, m), 7.76—7.81 (4H, m), 7.99 (1H, t, J=2 Hz). ^{19}F-NMR ($CDCl_3$) δ: −152.50 (1F, q, J=22 Hz). MS m/z: 272 (M^+), 227. HR-MS Calcd for $C_{16}H_{13}FO_3$ (M^+): 272.0849. Found: 272.0815.

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