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

Hidehito FUSISAWA,¹ Tomoya FUJIIWARA,¹ Yoshio TAKEUCHI,*,¹ and Kenji OMATA²

¹ Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University; Sugitani 2630, Toyama 930–0194, Japan; and ² Department of Chemistry, Graduate School of Science, Tohoku University; Aoba-ku, Aramaki, Sendai 980–8578, Japan. Received January 4, 2005; accepted February 15, 2005

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. Nonetheless, these agents are normally marketed as racemates. This is possible because it has been shown 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 Et₃N·3HF, respectively (Eqs. 1, 2). Or electrophilic fluorination of the enol silyl ether by treatment with lithium diisopropylamide (LDA) (Eq. 3). Laurent et al. reported the synthesis of 2-fluorinated ester 4a by electrochemical oxidation in fluorinating media (Eq. 4). 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 (FClO₃), according to the convenient procedure we have reported previously. A simple and general procedure for optical resolution of the 2-fluorinated acids 2 is also described.

Results and Discussion

We first attempted direct fluorination of carbanions derived from methyl ester 3a using selectfluor and N-fluorobenzensulfonimid. 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 FClO₃, considering the successful results obtained in the preparation of the structurally similar 2-cyano-2-fluoro-p-tolylacetic acid ethyl ester.

We first examined bases and temperatures for the fluorination of ibuprofen methyl ester 3a with FClO₃ 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 disopropylamine (LDA) by usual procedure, was subjected to slow introduction of diluted FClO₃ at ~40 °C for 1 h, to give α-fluorobuprofen 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-fluo esters 4b—d were obtained in excellent yields. In the case of 3e, however, formation of a complex mixture was observed. Since

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* To whom correspondence should be addressed.  e-mail: takeuchi@ms.toyama-mpu.ac.jp © 2005 Pharmaceutical Society of Japan
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 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 diastereomeric esters 8a—e and 9a—e, respectively. These diastereomeric esters were easily separated by column chromatography on silica gel (hexane/AcOEt=4/1 or CHCl3/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 ([α]D27 = 27.1°, c = 1.1, EtOH) was determined as R by comparison with the data of literature ([α]D24 = 22.6°, c = 1.2, EtOH).5) The diastereomers, 9b, 8c, and 8e, were recrystallized from hexane/AcOEt or hexane/CHCl3 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 CHCl3 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.

**Conclusion**

We have developed a simple procedure for preparation 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 CHCl3/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).

**Table 1.** Fluorination of Methyl Ester of Ibuprofen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Temperature</th>
<th>Time</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH (1.2 eq)</td>
<td>rt</td>
<td>2 h</td>
<td>SM recovery</td>
</tr>
<tr>
<td>2</td>
<td>KH (1.5 eq)</td>
<td>rt</td>
<td>1 h</td>
<td>SM recovery</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOK (1.2 eq)</td>
<td>rt</td>
<td>1 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>NHMDS (1.5 eq)</td>
<td>0 °C</td>
<td>1 h</td>
<td>&lt;25%</td>
</tr>
<tr>
<td>5</td>
<td>NHMDS (1.5 eq)</td>
<td>−40 °C</td>
<td>1 h</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>6</td>
<td>NHMDS (1.5 eq)</td>
<td>−78 °C</td>
<td>1 h</td>
<td>&lt;33%</td>
</tr>
<tr>
<td>7</td>
<td>LHMD (1.5 eq)</td>
<td>−78 °C</td>
<td>1 h</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>8</td>
<td>KHMD (1.5 eq)</td>
<td>−78 °C</td>
<td>1 h</td>
<td>&lt;38%</td>
</tr>
<tr>
<td>9</td>
<td>LDA (1.5 eq)</td>
<td>0 °C</td>
<td>1 h</td>
<td>&lt;12%</td>
</tr>
<tr>
<td>10</td>
<td>LDA (1.5 eq)</td>
<td>−40 °C</td>
<td>1 h</td>
<td>93% (isolated yield)</td>
</tr>
<tr>
<td>11</td>
<td>LDA (1.5 eq)</td>
<td>−78 °C</td>
<td>1 h</td>
<td>90% (isolated yield)</td>
</tr>
<tr>
<td>12a</td>
<td>LDA (1.5 eq)</td>
<td>−78 °C→rt</td>
<td>3 h</td>
<td>&lt;33%</td>
</tr>
</tbody>
</table>

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

![Chart 1](chart1.png)

![Chart 2](chart2.png)
the optically active 2-aryl-2-fluoropropionic acids by electrophilic fluorination of racemic 2-arylpropionic acid esters with FClO₃ 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 not corrected. 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 JAMS-X5 505 HAD; ¹H-NMR spectra, JEOL JNM-GX 270 (270 MHz) in CDCl₃ or CD₂OD with TMS (=0.00 ppm) as an internal standard; ¹³C-NMR spectra, JEOL JNM- GX 270 (254 MHz), in CDCl₃ or CD₂OD with CFCl₃ (=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 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 NaHCO₃ (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 MgSO₄, 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). ¹H-NMR (CDCl₃) 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 C₁₇H₂₁O₂ (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). ¹H-NMR (CDCl₃) 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, 9 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 C₁₇H₁₄FO₂ (M⁺): 244.1099. Found: 244.1053.

Methyl 2-(3-Fluoro-4-phenyl)phenylpropionate [(±)-3c]: Colorless oil. IR (neat) cm⁻¹: 1738 (C=O). ¹H-NMR (CDCl₃) 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). ¹F-NMR (CDCl₃) δ: −118.13 (1F, t, J=10 Hz). MS m/z: 258 (M⁺), 199. HR-MS Calcd for C₁₇H₁₃F₂O₂ (M⁺): 258.1056. Found: 258.1080.

Colorless oil. IR (neat) cm⁻¹: 1739 (C=O). ¹H-NMR (CDCl₃) 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 C₁₄H₁₅FO₂ (M⁺): 256.1099. Found: 256.1074.

Methyl 2-[3-(4-Phenylcarbonyl)phenyl]propionate [(±)-3e]: Colorless oil. IR (neat) cm⁻¹: 1738 (C=O). ¹H-NMR (CDCl₃) 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 C₁₅H₁₅F2O₂ (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 NaHCO₃ (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 MgSO₄, and concentrated. The residual oil was purified by column chromatography on silica gel (hexane/AcOEt = 4/1) to give methyl ester 3a in 95—100% yields.

Methyl 2-Fluoro-2-[4-(2-methylpropyl)phenyl]propionate [(±)-4a]: Colorless oil. IR (neat) cm⁻¹: 1743 (C=O). ¹H-NMR (CDCl₃) 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). ¹³C-NMR (CDCl₃) δ: −150.83 (1F, q, J=22 Hz). MS m/z: 238 (M⁺), 218, 179. HR-MS Calcd for C₁₇H₂₁FO₂ (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). ¹H-NMR (CDCl₃) 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=11 Hz), 7.89 (1H, d, J=11 Hz). ¹³C-NMR (CDCl₃) δ: −150.77 (1F, q, J=22 Hz). MS m/z: 262 (M⁺), 242, 203. HR-MS Calcd for C₁₇H₁₅F2O₂ (M⁺): 262.1005. Found: 262.0959.

Methyl 2-Fluoro-2-[3-(4-fluoro-4-phenyl)phenyl]propionate [(±)-4c]: Colorless needles (from hexane/CHCl₃), mp 67—70°C. IR (KBr) cm⁻¹: 1748 (C=O). ¹H-NMR (CDOD) δ: 1.96 (3H, d, J=2, 22 Hz), 3.81 (3H, s), 7.30—7.56 (8H, m). ¹³C-NMR (CDOD) δ: −117.26—−117.94 (1F, m), −152.38 (1F, q, J=22 Hz). MS m/z: 276 (M⁺), 217. HR-MS Calcd for C₁₉H₁₅F₂O₂ (M⁺): 276.0962. Found: 276.0962.
Methyl 2-Fluoro-2-(4-phenylphenyl)propionate ([z]-4d): Yellow oil. IR (neat) cm⁻¹: 1744 (C=O), 1730 (C=O). ¹H-NMR (CDCl₃) δ: 1.91 (3H, d, J=22 Hz), 3.77 (3H, s). 7.19—7.26 (3H, m), 7.30—7.38 (3H, m). ¹³F-NMR (CDCl₃) δ: −151.85 (1F, q, J=22 Hz). MS m/z: 274 (M⁺), 255, 215. HR-MS Calcd for C₃₃H₃₅FO₂: 274.0977. 274.0966. 

Preparation of Methyl 2-Fluoro-2-[3-(phenylcarbonyl)phenyl]propionate ([z]-5e): Colorless oil. IR (neat) cm⁻¹: 1742 (C=O). ¹H-NMR (CDCl₃) δ: 1.91 (3H, d, J=22 Hz), 3.74 (3H, s), 4.06 (2H, d, J=7 Hz), 7.28—7.37 (7H, m), 7.40—7.52 (4H, m), 7.71 (1H, t, J=22 Hz). ¹³F-NMR (CDCl₃) δ: −151.85 (1F, q, J=22 Hz). MS m/z: 330 (M⁺), 271. HR-MS Calcd for C₃₃H₃₅FO₂: 330.1267. Found: 330.1256.

Preparation of Methyl 2-Fluoro-2-[3-(phenylcarbonyl)phenyl]propionate ([z]-6f): Colorless oil. IR (neat) cm⁻¹: 1742 (C=O). ¹H-NMR (CDCl₃) δ: 1.91 (3H, d, J=22 Hz), 3.74 (3H, s), 4.06 (2H, d, J=7 Hz), 7.28—7.37 (7H, m), 7.40—7.52 (4H, m), 7.71 (1H, t, J=22 Hz). ¹³F-NMR (CDCl₃) δ: −151.85 (1F, q, J=22 Hz). MS m/z: 330 (M⁺), 271. HR-MS Calcd for C₃₃H₃₅FO₂: 330.1267. Found: 330.1256.

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 CH₂Cl₂ (20 ml×3). The organic layer was washed with brine and dried over Na₂SO₄. After the solvent was evaporated, the residual oil was purified by column chromatography on silica gel (hexane:AcOEt=4:1) to give 2-fluorinated esters 4e in 93% yield. Colorless oil. IR (neat) cm⁻¹: 1661 (C=O), 1744 (C=O). ¹H-NMR (CDCl₃) δ: 1.97 (3H, d, J=22 Hz), 3.78 (3H, s), 7.46—7.76 (4H, m), 7.73—7.81 (4H, m). 7.96 (1H, J=2 Hz). ¹³F-NMR (CDCl₃) δ: −152.43 (1F, q, J=22 Hz). MS m/z: 322 (M⁺), 274. HR-MS Calcd for C₂₃H₂₃FO₃: 330.1267. Found: 330.1265.

Preparation of Methyl 2-Fluoro-2-[4-(2-methylpropyl)phenyl]propionate ([z]-9a—e): Ten percent aqueous HCl (5 ml) was added to a solution of 2-aryl-2-fluoropropanoic acids 2a—e (562 mg, 1.7 mmol) in MeOH (5 ml) and the mixture was stirred at room temperature for 18 h. Saturated aqueous NaHCO₃ 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 Na₂SO₄. After the solvent was evaporated, the residual oil was purified by column chromatography on silica gel (hexane:AcOEt=6:1) to give methyl esters 9a—e in 33% yield. Colorless oil. IR (neat) cm⁻¹: 1739 (C=O), 1351 (OH). ¹H-NMR (CDCl₃) δ: 0.65—0.77 (2H, m), 0.96 (3H, s), 0.99 (3H, s), 1.05 (3H, s), 1.15—1.25 (2H, m), 1.25—1.63 (2H, m), 2.02—1.69 (1H, m), 1.55—1.68 (1H, m). 3.48 (1H, d, J=8 Hz), 5.47 (1H, d, J=8 Hz), 7.12 (1H, d, J=8 Hz), 7.17 (1H, d, J=8 Hz), 7.20 (1H, d, J=8 Hz). ¹³C-NMR (CDCl₃) δ: −151.47 (1F, q, J=22 Hz). MS m/z: 215 (M⁺), 126. HR-MS Calcd for C₁₆H₁₅FO₃: 276.414. Found: 276.420.
Fluoro-2-[4-(phenacyl)phenyl]propionate (8d): Colorless oil. IR (neat) cm⁻¹: 1739 (C=O), 3453 (OH). ¹H-NMR (CDCl₃): 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, d, J=8, 10 Hz), 6.94-7.10 (3H, m), 7.11-7.24 (3H, m), 7.26-7.37 (1H, m). ¹³C-NMR (CDCl₃): δ: -150.33 (1F, q, J=22 Hz). MS m/z: 424 (M⁺), 394. HR-MS Measured for C₂₆H₂₉FO₄ (M⁺): 424.2050. Found: 424.2079.

Fluoro-2-[4-(phenacyl)phenyl]propionate (9d): Colorless oil. IR (neat) cm⁻¹: 1741 (C=O), 3495 (OH). ¹H-NMR (CDCl₃): 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, d, J=8, 10 Hz), 6.94-7.02 (3H, m), 7.09-7.23 (3H, m), 7.31-7.37 (1H, m). ¹³C-NMR (CDCl₃): δ: -150.90 (1F, q, J=22 Hz). MS m/z: 412 (M⁺), 394. HR-MS Measured for C₂₆H₂₉FO₄ (M⁺): 412.2050. Found: 412.2074.

(1R,2R,3R,6S)-4-Hydroxy-4,7-trimethyl-bicyclo[4.1.0]hept-3-yl (21): Colorless oil (AcOEt or MeOH/acetone (1:1)). ¹H-NMR (CDCl₃): δ 1.15 (3H, s), 1.18 (3H, s), 1.54-1.66 (1H, m), 7.46-7.53 (3H, m), 7.58-7.62 (1H, m), 7.72-7.81 (4H, m), 7.98 (1H, t, J=12 Hz). ¹³C-NMR (CDCl₃): δ: -151.81 (1F, q, J=22 Hz). MS m/z: 424 (M⁺). 406. HR-MS Measured for C₂₆H₂₉FO₄ (M⁺): 424.2050. Found: 424.2080.

Preparation of Chiral 2-Aryl-2-fluorophenylacetic Acids 2a-e by Hydrolysis of Esters 8 or 9: 1st KOH (1.5 ml) was added to a solution of esters of 8 or 9 (1.0 mmol) in MeOH (5 ml) was added 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), acidified with 10% HCl (pH 1) and extracted with CH₂Cl₂ (20 ml x 3). The organic layer was washed with brine and dried over MgSO₄. After evaporation of the solvent, the residual oil was purified by column chromatography on silica gel (AcOEt or MeOH:acetone=1:9) to give chiral 2-aryl-2-fluorophenylacetic acids 2a-e (mp 158-197°C).

(R)-(-)2a: Colorless solid (from hexane/AcOEt). mp 164-165°C. [α]D₂⁰ +27.1° (c=1.1, EtOH). IR (KBr) cm⁻¹: 1716 (C=O), 3421 (OH). ¹H-NMR (CDCl₃): 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). ¹³C-NMR (CDCl₃): δ: -149.46 (1F, q, J=22 Hz). MS m/z: 224 (M⁺). 179. HR-MS Measured for C₁₅H₁₉F₂O₂ (M⁺): 224.1213. Found: 224.1201.

(S)(+)-2a: Colorless solid (from hexane/AcOEt). mp 159-163°C. [α]D₂⁰ +30.6° (c=1.0, EtOH). IR (KBr) cm⁻¹: 1716 (C=O), 3431 (OH). ¹H-NMR (CDCl₃): 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). ¹³C-NMR (CDCl₃): δ: -149.46 (1F, q, J=22 Hz). MS m/z: 224 (M⁺). 179. HR-MS Measured for C₁₅H₁₉F₂O₂ (M⁺): 224.1213. Found: 224.1222.

(R)-(-)2b: Colorless crystals (from hexane/AcOEt). mp 113-115°C. [α]D₂⁰ +46.9° (c=1.0, MeOH). IR (KBr) cm⁻¹: 1739 (C=O), 3442 (OH). ¹H-NMR (CDCl₃): δ 2.04 (3H, d, J=22 Hz), 3.91 (3H, s), 7.11-7.18 (2H, m), 7.57 (1H, d, J=2, 9 Hz), 7.73 (1H, s), 7.76 (1H, s), 7.92 (1H, d, J=11 Hz). ¹³C-NMR (CDCl₃): δ: -150.16 (1F, q, J=22 Hz). MS m/z: 248 (M⁺). 203. HR-MS Measured for C₁₅H₁₉F₂O₂ (M⁺): 248.0849. Found: 248.0837.

(S)(+)-2b: Colorless crystals (from hexane/AcOEt). mp 112-115°C. [α]D₂⁰ +46.9° (c=1.0, MeOH). IR (KBr) cm⁻¹: 1737 (C=O), 3447 (OH). ¹H-NMR (CDCl₃): δ 2.04 (3H, d, J=22 Hz), 3.91 (3H, s), 7.11-7.18 (2H, m), 7.57 (1H, d, J=2, 9 Hz), 7.73 (1H, s), 7.76 (1H, s), 7.92 (1H, d, J=11 Hz). ¹³C-NMR (CDCl₃): δ: -150.16 (1F, q, J=22 Hz). MS m/z: 248 (M⁺).