Pergamon

Tetrahedron 55 (1999) 12741–12750

TETRAHEDRON

SYNTHESIS OF 2-FLUORO ANALOG OF 6-AMINONORBORNANE -2,6-DICARBOXYLIC ACID: A CONFORMATIONALLY RIGID GLUTAMIC ACID DERIVATIVE

Hisanaka Ito, Akio Saito, Akito Kakuuchi, and Takeo Taguchi*

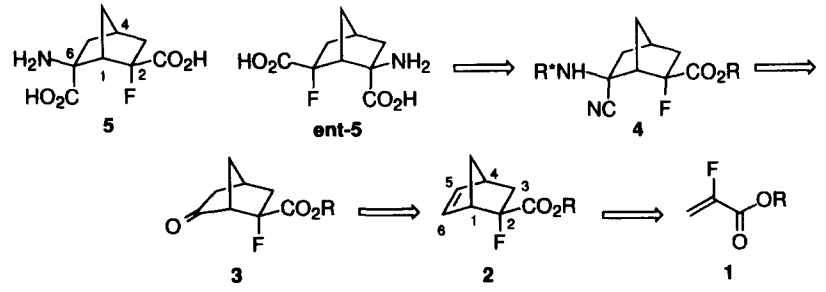
Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

Received 28 June 1999; accepted 2 September 1999

Abstract: Synthesis of 2-fluoro analog of 6-aminonorbornane-2,6-dicarboxylic acid, a conformationally restricted analog of glutamic acid, in optically pure form is described.

Conformationally restricted analogs of L-glutamate, an excitatory neurotransmitter, have been recognized to serve as useful tools for elucidating the conformational requirement (extended or folded form *e.g.*) for the L-glutamate receptor subtype specificity. Among the recent advances in this field, it should be noted that the glutamate analogs conformationally restricted by introducing cyclopropane ring [(2*S*,3*S*,4*S*)-2-(carboxycyclopropyl)glycine (L-CCG-I)][1] or bicyclic ring systems [2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740)[2] and 2-aminobicyclo[2.1.1]hexane-2,6-dicarboxylic acid[3]] were found to be potent and selective agonists of metabotropic glutamate receptors (mGluRs) and it was suggested that the extended conformation of L-glutamate is possibly the active conformation for mGluRs. In addition to such structural designs, displacement of the carboxyl group to phosphonoyl group[4] or introduction of fluorine[5] to alter the property of the functional group (for example enhancement of acidity) is also an important modification of glutamate. Related to our fluorine-modified glutamate chemistry,[5] we have reported the Lewis acid mediated Diels-Alder reaction of 2-fluoroacrylate.[6,7] In particular, excellent diastereo- and *exo*-selectivities with cyclopentadiene could be achieved on using 8-phenylmenthyl group as a chiral auxiliary.[7] In this paper, we report the preparation of 2-fluoro analog of 6-aminonorbornane-2,6-dicarboxylic acid **5**, a conformationally restricted analog of glutamate, using the Diels-Alder adduct of 2-fluoroacrylate with cyclopentadiene as the starting material. The synthetic route we planed involves 1) conversion of the Diels-Alder adduct **2** to 6-keto compound **3** through hydroboration-oxidation of the double bond which would hopefully proceed in a regioselective manner to some extent due to the inductive effect of fluorine and ester

Scheme 1



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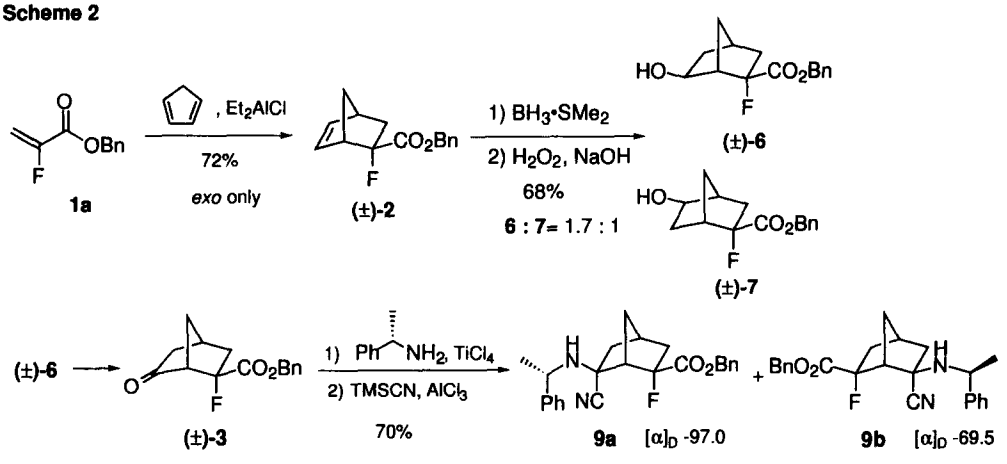
groups at 2 position,[8,9] and 2) construction of amino acid moiety through the amino nitrile **4** derived from racemic 6-keto compound **3** with a chiral amine, so that the optical resolution would be possible by the separation of the diastereomers (Scheme 1).

The Diels-Alder reaction of benzyl 2-fluoroacrylate **1a** with cyclopentadiene in the presence of Et_2AlCl (1.1 equiv) proceeded in an *exo*-selective manner to give the adduct (±)-**2** in 72% yield.[6] Hydroboration of the Diels-Alder adduct (±)-**2** (BH_3•SMe_2 then 30% H_2O_2, NaOH, 68%) gave a mixture of the regioisomers of *exo*-alcohol (±)-**6** and (±)-**7** in a 1.7 : 1 ratio.[10] Due to the similar regioselectivity in hydroboration of the non-fluorinated substrate, methyl bicyclo[2.2.1]hept-5-ene-2*exo*-carboxylate, giving rise to a mixture of 6*exo*-and 5*exo*-alcohol in a ratio of 1.5 : 1,[8a] the effect of fluorine at 2-position on the regioselectivity was not significant, although the preferable attack of borone to C-6 relative to C-5 is possibly explained by the inductive effect of C-2 substituents.[8] Oxidation of (±)-**6** with Dess-Martin periodinane gave the ketone (±)-**3**.[11] With the ketone (±)-**3**, the Bucherer hydantoin synthesis (KCN, $(NH_4)_2CO_3$) or the Strecker reaction (KCN, NH_4Cl in NH_4OH) didn't work even at 120 °C in a sealed tube. Thus, the existence of *endo*-fluorine sustituent at 2-position hindered both reactions, since the similar substrates without fluorine smoothly react under the milder conditions.[12] To solve this low reactivity of the carbonyl group and to achieve the optical resolution of the amino nitrile compound, we tried the two step reactions using *S*-(-)-1-phenylethylamine. That is, the reaction of (±)-**3** with *S*-(-)-1-phenylethylamine in the presence of $TiCl_4$ gave the crude imine compound after extractive work-up,[13] which was reacted with trimethylsilylcyanide in the presence of $AlCl_3$[14] to give two isomers of the amino nitrile **9a** (31%) and **9b** (39%). Separation of these isomers was carried out by column chromatography. As shown in Fig. 1, the relative stereochemistry of **9** was determined by X-ray analysis of (+)-**12** obtained by hydrogenolysis of **9b** followed by esterification with CH_2N_2 to reveal that cyanide attacks the imino group exclusively from the concave face to form the *exo*-amino compound.

Scheme 2



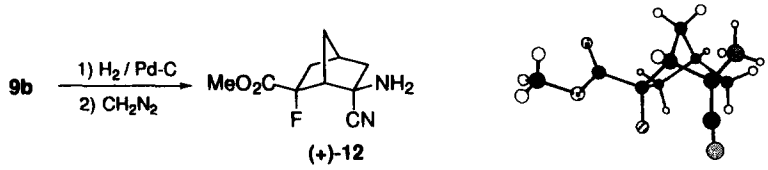
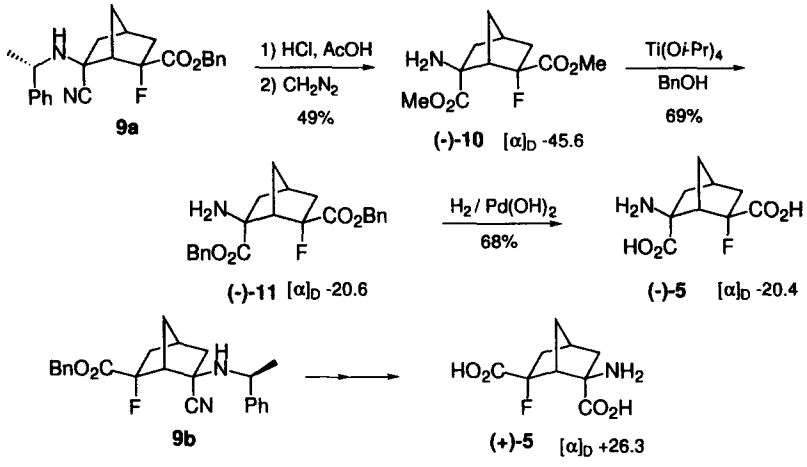


Fig. 1 Chem3D Drawing of (+)-12 based on the X-ray crystallographic analysis

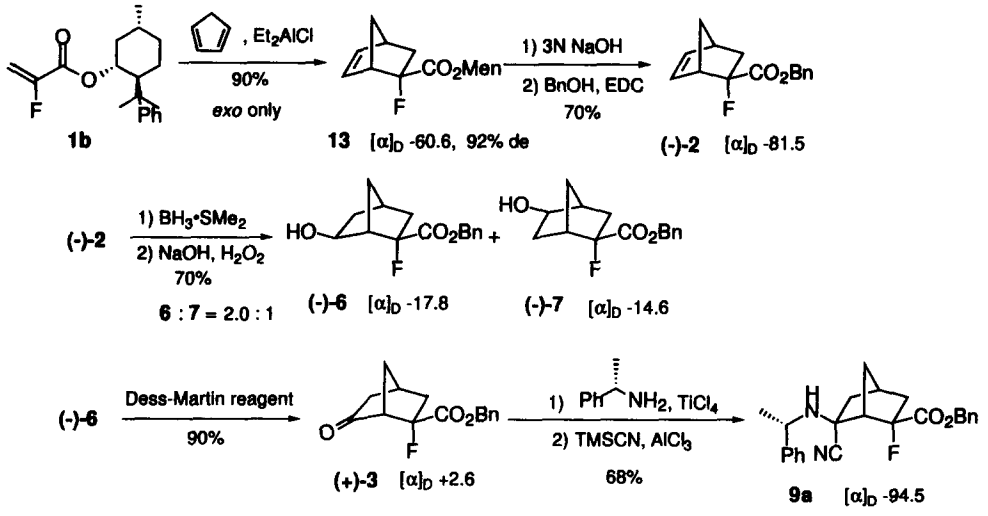
Conversion of the diastereomerically pure amino nitrile **9a** to the amino acid **5** was achieved as follows. While alkaline hydrolysis was accompanied by defluorination, hydrolysis of nitrile and benzyl ester as well as *N*-debenzylation of **9a** proceeded by treating with HCl in acetic acid at 160 °C (sealed tube) to give the dimethyl ester (-)-**10** in 49% yield after treating with CH_2N_2. For the ease in purification procedure of the amino acid form, hydrogenation of dibenzyl ester **11** was employed. Thus, ester exchange reaction of (-)-**10** with benzyl alcohol in the presence of $Ti(O\textit{i}\text{-}Pr)_4$ gave dibenzyl ester (-)-**11**, which was debenzylated (H_2, 5% $Pd(OH)_2$ in AcOEt) to give the desired amino acid (-)-**5**. In a similar manner, (+)-**5** (**ent**-(-)-**5**) was prepared from **9b** (Scheme 3).

Scheme 3



The absolute configuration was determined by synthesizing the amino nitrile **9** using the optically active 6-keto compound **3** derived from the Diels-Alder reaction of 8-phenylmenthyl 2-fluoroacrylate (Scheme 4). Thus, the Diels-Alder adduct **13** (*exo* only, 90% yield, 92% de) obtained from (1*R*,2*S*,5*R*)-8-phenylmenthyl 2-fluoroacrylate **1b** with cyclopentadiene[7] was converted to the benzyl ester (-)-**2** having (1*S*,2*S*,4*S*)-configuration. In a similar procedure for the preparation of racemic **3**, the benzyl ester (-)-**2** gave the ketone (+)-**3** through hydroboration and oxidation. Formation of the imine from (+)-**3** and *S*-(-)-1-phenylethylamine followed by the cyanide addition provided a single isomer of the amino nitrile ($[\alpha]_D$ -94.5), which was identical with **9a**, one of the isomers prepared from raccemic **3**. Since the absolute configuration of (-)-**2** was determined to be 1*S*,2*S*,4*S*,[7] **9a** and (-)-**5** prepared from **9a** should have (1*S*,2*S*,4*S*,6*S*)-configuration.

Scheme 4



Regarding the neuropharmacological activity, both enantiomers (+)-**5** and (-)-**5** at 10^{-3} M didn't cause significant depolarization responses in the isolated spinal cord of newborn rats.[15] This result may indicate that the glutamate analog **5** havig the *exo*-amino group is possibly conformationally inactive at the glutamate receptor site. Preparation of the stereoisomer having the *endo*-amino group, corresponding to the fixed extended conformer of glutamate, is our current subject.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan. A generous donation of benzyl 2-fluoroacrylate by Daikin Industies, Ltd. is gratefully acknowledged. The authors thank Mr. H. Fukaya of our university for X-ray analysis and Dr. H. Shinozaki of Tokyo Metropolitan Institute of Medical Science for pharmacological evaluation.

Experimental

General: ^{1}H- and ^{13}C-NMR spectra were taken on a Brucker AM400 or a Varian Gemini-300 spectrometer, and chemical shifts were reported in parts per million (ppm) using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^{1}H-NMR, and $CDCl_3$ (77.01 ppm) for ^{13}C-NMR as an internal standard, respectively. ^{19}F-NMR spectra were taken on a Brucker AM400 spectrometer, and chemical shifts were reported in parts per million (ppm) using benzotrifluoride as a standard. Infrared spectra (IR) were recorded on a JASCO FTIR-620 infrared spectrophotometer. Mass spectra (MS) were obtained on a Hitachi M-80, Finnigan MAT TSQ700 or VG Auto spec. Optical rotations were recorded on a JASCO DIP-360 polarimeter. Medium pressure liquid chromatography (MPLC) was performed using prepacked column (silica gel, 50 μm) with UV or RI detector.

Benzyl (1*S,2*S**,4*S**)-2-fluorobicyclo[2.2.1]hept-5-ene-2-carboxylate (±)-2**

Under an argon atmosphere to a mixture of benzyl 2-fluoroacrylate (8.0 g, 42.8 mmol) and

cyclopentadiene (6.6 mL, 68.5 mmol) in CH_2Cl_2 (40 mL) cooled at -78 ℃ was added diethylaluminum chloride (0.96 M hexane solution, 49.0 mL, 47.0 mmol) and the whole was stirred for 2.5 h at -78 ℃ and for 3 h at 0 ℃. The reaction mixture was extracted with AcOEt after addition of sat.NH_4Cl aq. The extract was washed with brine, dried over $MgSO_4$, and concentrated to leave the residue, which was chromatographed (SiO_2, hexane : AcOEt = 25 : 1) to give (±)-**2** (7.77 g, 72 %) as a colorless oil. IR (neat) νcm^{-1}; 1739. ^1H NMR (300 MHz, $CDCl_3$) δ; 7.42-7.39 (5H, m), 6.48 (1H, dd, *J* = 5.6, 3.0 Hz), 6.10 (1H, dd, *J* = 5.6, 3.0 Hz), 5.27 (2H, s), 3.22 (1H, brs), 2.98 (1H, brs), 2.40 (1H, ddd, *J* = 13.1, 13.1, 3.6 Hz), 1.85 (1H, brd, *J* = 9.1 Hz), 1.62-1.42 (1H, m), 1.47 (1H, ddd, *J* = 24.3, 13.1, 4.1 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ; 40.4 (d, *J* = 20.0 Hz), 42.6, 49.3, 51.9 (d, *J* = 21.5 Hz), 67.7, 101.4 (d, *J* = 195.5 Hz), 128.6, 128.8, 129.0, 132.8, 135.8, 140.6, 166.4 (d, *J* = 27.3 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; -94.6 (dd, *J* = 24.3, 13.1 Hz). EI-MS *m/z*: 246 (M^+). HRMS calcd for $C_{15}H_{15}FO_2$: 246.1056 (M^+). Found: 246.1063.

Benzyl (1*S,2*S**,4*S**,6*S**)-2-fluoro-6-hydroxybicyclo[2.2.1]heptane-2-carboxylate (±)-6 and Benzyl (1*S**,2*S**,4*S**,5*R**)-2-fluoro-5-hydroxybicyclo[2.2.1]heptane-2-carboxylate (±)-7**

Under an argon atmosphere a mixture of (±)-**2** (3.5 g, 13.9 mmol) and BH_3•Me_2S (10.0 M in hexane, 0.53 mL, 5.3 mmol) in hexane (35 mL) was stirred for 5 min at rt, then to this was added THF (12 mL) and the whole was stirred for 4 h. To the mixture cooled by ice-bath were successively added dioxane (12 mL), 3N NaOH (3.6 mL) and 30% H_2O_2 (1.8 mL). After being stirred for 20 min and then the addition of brine, the reaction mixture was extracted with AcOEt, which was dried over $MgSO_4$ and concentrated. The residue was chromatographed (SiO_2, hexane : AcOEt = 5 : 1) to give (±)-**6** (1.62 g, 43%) and (±)-**7** (0.94 g, 25%).

(±)-**6**: colorless oil. IR (neat) νcm^{-1}; 3387, 1738. ^1H NMR (400 MHz, $CDCl_3$) δ; 7.40-7.31 (5H, m), 5.25 (1H, d, *J* = 12.3 Hz), 5.21 (1H, d, *J* = 12.3 Hz), 4.44 (1H, d, *J* = 6.6 Hz), 2.62 (1H, brs), 2.39 (1H, brs), 2.32 (1H, dddd, *J* = 18.0, 13.9, 4.4, 2.9 Hz), 1.95 (1H, ddd, *J* = 13.5, 6.6, 2.3 Hz), 1.80 (1H, brd, *J* = 10.7 Hz), 1.72 (1H, brd, *J* = 10.7 Hz), 1.65 (1H, brs), 1.49 (1H, brd, *J* = 13.5 Hz), 1.43 (1H, ddd, *J* = 26.0, 13.9, 3.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 35.5 (d, *J* = 2.6 Hz), 35.8, 41.1 (d, *J* = 23.3 Hz), 41.1, 53.6 (d, *J* = 17.7 Hz), 67.7, 68.0 (d, *J* =15.9 Hz), 99.1 (d, *J* = 198.0 Hz), 128.6, 128.9, 129.1, 135.7, 171.8 (d, *J* = 29.0 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; -105.0 (dd, *J* = 26.0, 18.0 Hz). EI-MS *m/z*: 264 (M^+). HRMS calcd for $C_{15}H_{17}FO_3$: 264.1162 (M^+). Found: 264.1173. Anal. Calcd for $C_{15}H_{17}FO_3$: C, 68.17; H, 6.48. Found: C, 67.91; H, 6.53.

(±)-**7**: colorless oil. IR (neat) νcm^{-1}; 3387, 1737. ^1H NMR (400 MHz, $CDCl_3$) δ; 7.37-7.32 (5H, m), 5.24 (1H, d, *J* = 12.3 Hz), 5.20 (1H, d, *J* = 12.3 Hz), 3.98 (1H, dd, *J* = 6.8, 2.0 Hz), 2.61 (1H, d, *J* = 3.6 Hz), 2.42 (1H, dd, *J* = 13.8, 6.8 Hz), 2.33 (1H, ddd, *J* = 16.2, 14.2, 5.1 Hz), 2.24 (1H, d, *J* = 5.1 Hz), 1.80-1.60 (3H, m), 1.36 (1H, ddd, *J* = 25.4, 14.2, 3.3 Hz), 1.32-1.23 (1H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 34.0 (d, *J* = 11.7 Hz), 34.2 (d, *J* = 2.8 Hz), 37.3 (d, *J* = 23.9 Hz), 43.9, 44.8 (d, *J* =19.5 Hz), 67.2, 72.8, 98.5 (d, *J* = 198.5 Hz), 128.1, 128.4, 128.6, 135.6, 171.7 (d, *J* = 29.7 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; -101.3 (dd, *J* = 25.4, 16.2 Hz). EI-MS *m/z*: 264 (M^+). HRMS calcd for $C_{15}H_{17}FO_3$: 264.1162 (M+). Found: 264.1150. Anal. Calcd for $C_{15}H_{17}FO_3$: C, 68.17; H, 6.48. Found: C, 67.92; H, 6.55.

Benzyl (1*S,2*S**,4*S**)-2-fluoro-6-oxobicyclo[2.2.1]heptane-2-carboxylate (±)-3**

Under argon atmosphere a mixture of (±)-**6** (472.0 mg, 1.74 mmol) and Dess-Martin reagent (4.4 g,

10.4 mmol) in CH_2Cl_2 (15 mL) was stirred for 1.5 h at rt. The reaction mixture was extracted with AcOEt after addition of sat $NaHCO_3$ aq and the extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed (SiO_2, hexane : AcOEt = 4 : 1) to give (±)-**3** (463 mg, 99%) as a colorless oil. IR (neat) νcm^{-1}; 1750. ^1H NMR (400 MHz, $CDCl_3$) δ; 7.38-7.33 (5H, m), 5.27 (1H, d, *J* = 12.2 Hz), 5.23 (1H, d, *J* = 12.2 Hz), 3.02 (1H, brs), 2.80 (1H, brs), 2.55 (1H, dddd, *J* = 18.8, 14.1, 4.4, 2.9 Hz), 2.27 (1H, ddd, *J* = 17.9, 4.7, 2.9 Hz), 2.20-2.08 (2H, m), 1.96 (1H, ddd, *J* = 24.8, 14.1, 3.7 Hz) 1.87-1.80 (1H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 33.0, 37.6 (d, *J* = 3.5 Hz), 40.1 (d, *J* = 23.4 Hz), 43.0, 58.4 (d, *J* =21.6 Hz), 67.2, 97.0 (d, *J* = 198.2 Hz), 127.8, 128.2, 128.3, 134.6, 169.3 (d, *J* = 28.6 Hz), 208.8 (d, *J* = 8.7 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; -90.8 (dd, *J* = 24.8, 18.8 Hz). EI-MS *m/z*: 262 (M^+). Anal. Calcd for $C_{15}H_{15}FO_3$: C, 68.69; H, 5.76. Found: C, 68.89; H, 5.87.

Benzyl (1*S*, 2*S*, 4*S*, 6*S*)- and (1*R*, 2*R*, 4*R*, 6*R*)-6-cyano-2-fluoro-6-[(1*S*)-(1-phenylethyl)amino] bicyclo[2.2.1]heptane-2-carboxylate (9a and 9b)

Under an argon atmosphere to a mixture of (±)-**3** (133 mg, 0.49 mmol) and (*S*)-(-)-1-phenyethylamine (0.25 mL, 2.0 mmol) in benzene (2.0 mL) was added a benzene solution of $TiCl_4$ (2.0 M, 0.17 mL, 0.34 mmol) at 0 ℃ and the mixture was stirred for 4 h at rt. The reaction mixture was quenched by the addition of brine and extracted with ether. The extract was dried over $MgSO_4$, and then concentrated under vacuum to give the crude imine compound. To the crude imine compound disolved in benzene (3 mL) was added TMSCN (0.18 mL, 1.5 mmol) and $AlCl_3$ (65 mg, 0.49 mmol), and the mixture was stirred for 4 h at rt. Addition of H_2O, extraction with ether followed by the separation by column chromatography (SiO_2, hexane : AcOEt =15: 1) gave **9a** (50 mg, 31%) and **9b** (65 mg, 39%) along with the recovery of (±)-**3** (20 mg).

9a: colorless crystals. mp 78-80 ℃ (from AcOEt-hexane). $[\alpha]_D^{28}$ -97.0 (c 0.99, $CHCl_3$). IR (KBr) νcm^{-1}; 3325, 2218, 1744. ^1H NMR (400 MHz, $CDCl_3$) δ; 7.34-7.16 (10H, m), 5.21 (1H, d, *J* = 13.0 Hz), 5.18 (1H, d, *J* = 13.0 Hz), 4.13 (1H, q, *J* = 6.7 Hz), 2.81 (1H, brs), 2.38-2.25 (1H, m), 2.25-2.15 (2H, m), 1.70-1.57 (3H, m), 1.54 (1H, ddd, *J* = 26.0, 14.1, 4.0 Hz), 1.35 (3H, d, *J* = 6.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 25.9, 35.5, 36.4, 40.9 (d, *J* = 23.5 Hz), 42.0, 54.4, 54.9 (d, *J* = 15.6 Hz), 56.3 (d, *J* = 4.3 Hz), 67.5, 98.3 (d, *J* = 203.6 Hz), 122.0, 126.5, 127.0, 128.1, 128.5, 128.5, 128.6, 135.0, 146.3, 170.1 (d, *J* = 27.7 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; -98.9 (dd, *J* = 26.0, 16.0 Hz). EI-MS *m/z*: 377 (M^+-CH3). Anal. Calcd for $C_{24}H_{25}FN_2O_2$: C, 73.45; H, 6.42; N, 7.14. Found: C, 73.34; H, 6.53; N, 7.11.

9b: colorless crystals. mp 132-135 ℃ (from AcOEt-hexane). $[\alpha]_D^{28}$ -69.5 (c 0.96, $CHCl_3$). IR (KBr) νcm^{-1}; 3347, 2218, 1744. ^1H NMR (400 MHz, $CDCl_3$) δ; 7.35-7.18 (10H, m), 5.07 (2H, s), 4.17 (1H, q, *J* = 6.7 Hz), 2.42-2.28 (2H, m), 2.26 (1H, brs), 2.21 (1H, dd, *J* = 13.1, 2.1 Hz), 1.99 (1H, brd, *J* = 11.0 Hz), 1.78 (1H, ddd, *J* = 13.1, 3.8, 3.8 Hz) 1.57 (1H, ddd, *J* = 25.0, 13.5, 4.1 Hz), 1.40 (1H, d, *J* = 6.7 Hz) 1.35 (1H, brd, *J* = 11.0 Hz), 1.28 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 26.6, 35.5, 35.9, 41.3 (d, *J* = 23.6 Hz), 46.4, 52.0 (d, *J* = 15.8 Hz), 56.6, 57.2 (d, *J* = 5.2 Hz), 67.8, 98.5 (d, *J* = 202.9 Hz), 122.6, 127.1, 127.6, 128.4, 128.8, 128.8, 129.0, 135.4, 146.3 170.5 (d, *J* = 27.7 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; -99.5 (dd, *J* = 25.0, 17.0 Hz). EI-MS *m/z*: 377 (M^+-CH3). Anal. Calcd for $C_{24}H_{25}FN_2O_2$: C, 73.45; H, 6.42; N, 7.14. Found: C, 73.28; H, 6.46; N, 7.06.

Dimethyl (1*S*, 2*S*, 4*S*, 6*S*)-6-amino-2-fluorobicyclo[2.2.1]heptane-2,6-dicarboxylate (-)-10

After a mixture of **9a** (45 mg, 0.11 mmol) and c-HCl (5 mL) in AcOH (2.5 mL) in a sealed tube was

heated for 29 h at 110 ℃ and then for 12 h at 150 ℃, the mixture was concentrated under vacuum. To a solution of the residue in MeOH (2 mL) was added an ethereal solution of diazomethane and the following purification by column chromatography (SiO_2, hexane : AcOEt =2: 1) gave (-)-**10** (14 mg, 49%) as colorless crystals. mp 46-48 ℃ (from Et_2O-hexane). $[\alpha]_D^{24}$ -45.6 (c 0.32, $CHCl_3$). IR (KBr) νcm^{-1}; 3377, 3312, 1739. ^1H NMR (400 MHz, $CDCl_3$) δ; 3.78 (3H, s), 3.70 (3H, s), 2.73 (1H, bs), 2.43-2.35 (2H, m), 2.29 (1H, dddd, J = 18.0, 13.9, 4.5, 2.8 Hz) 2.16 (1H, brd, J = 10.9 Hz), 1.78 (1H, d, J = 10.9 Hz), 1.56 (1H, ddd, J = 26.0, 13.8, 4.2 Hz), 1.45 (1H, ddd, J = 13.4, 4.8, 2.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 35.2, 37.0, 39.4, 40.9 (d, J = 23.9 Hz), 52.2, 52.8, 55.8 (d, J = 16.5 Hz), 61.6 (d, J = 6.6 Hz), 99.1 (d, J = 199.3 Hz), 171.6 (d, J = 28.8 Hz), 175.9. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; -98.1 (dd, J = 26.0, 18.0 Hz). ESI-MS *m/z*: 246 (M^++H^+). FAB-MS calcd for $C_{11}H_{16}FNO_4$+H^+: 246.1142. Found: 246.1158. Anal. Calcd for $C_{11}H_{16}FNO_4$: C, 53.85; H, 6.58; N, 5.71. Found: C, 53.96; H, 6.48; N, 5.71.

Dimethyl (1*R*, 2*R*, 4*R*, 6*R*)-6-amino-2-fluorobicyclo[2.2.1]heptane-2,6-dicarboxylate (+)-10

In a similar manner for the synthesis of (-)-**10**, (+)-**10** was obtained in 54 % yield from **9b** (118 mg, 0.3 mmol). (+)-**10**: colorless crystals. $[\alpha]_D^{23}$ +32.7 (c 0.22, $CHCl_3$).

Dibenzyl (1*S*, 2*S*, 4*S*, 6*S*)-6-amino-2-fluorobicyclo[2.2.1]heptane-2,6-dicarboxylate (-)-11

A mixture of (-)-**10** (57 mg, 0.23 mmol) and Ti(O*i*-Pr)$_4$ (0.2 mL, 0.7 mmol) in benzyl alcohol (4.5 mL) was stirred for 15 h at 120 ℃. Purification by column chromatography (SiO_2, hexane : AcOEt =1: 1) gave (-)-**11** (64 mg, 69%) as colorless solid. mp 86-88 ℃. $[\alpha]_D^{21}$ -20.6 (c 0.66, $CHCl_3$). IR (KBr) νcm^{-1}; 3390, 1736. ^1H NMR (400 MHz, $CDCl_3$) δ; 7.40-7.26 (10H, m), 5.23 (2H, s), 5.08 (2H, s), 2.78 (1H, brs), 2.48-2.29 (3H, m), 2.17 (1H, brd, J = 10.9 Hz), 1.77 (1H, brd, J = 10.9 Hz), 1.60 (1H, ddd, J = 25.9, 13.0, 4.1 Hz), 1.48 (1H, ddd, J = 13.3, 4.2, 3.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 35.2, 36.9 (d, J = 2.5 Hz), 39.4, 40.7 (d, J = 23.8 Hz), 55.7 (d, J = 16.6 Hz), 61.7 (d, J = 6.5 Hz), 66.9, 67.3, 99.2 (d, J = 199.5 Hz), 128.0, 128.1, 128.3, 128.4, 128.6, 135.3, 135.9, 170.9 (d, J = 28.6 Hz), 175.1. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; -97.2 (dd, J = 25.9, 21.0 Hz). FAB-MS *m/z*: 398 (M^++H^+). Anal. Calcd for $C_{23}H_{24}FNO_4$: C, 69.51; H, 6.09; N, 3.52. Found: C, 69.25; H, 6.20; N, 3.50.

Dibenzyl (1*R*, 2*R*, 4*R*, 6*R*)-6-amino-2-fluorobicyclo[2.2.1]heptane-2,6-dicarboxylate (+)-11

A mixture of (+)-**10** (39 mg, 0.16 mmol) and Ti(O*i*-Pr)$_4$ (0.14 mL, 0.47 mmol) in benzyl alcohol (3 mL) was stirred for 15 h at 120 ℃. Purification by column chromatography (SiO_2, hexane : AcOEt =1: 1) gave (+)-**11** (32 mg, 51%) as colorless solid. $[\alpha]_D^{22}$ +19.5 (c 0.27, $CHCl_3$).

(1*S*, 2*S*, 4*S*, 6*S*)-6-Amino-2-fluorobicyclo[2.2.1]heptane-2,6-dicarboxylic acid (-)-5

Under a hydrogen atmosphere a mixture of (-)-**11** (43 mg, 0.11 mmol) and 5% $Pd(OH)_2$ (10 mg) in AcOEt (4 mL) was stirred for 8 h at rt. Purification by column chromatography (ODS, H_2O : acetonitrile =9 : 1) gave (-)-**5** (16 mg, 68%) as colorless solid. dec 202 ℃. $[\alpha]_D^{24}$ -20.4 (c 0.23, H_2O). IR (KBr) νcm^{-1}; 3421, 1729. ^1H NMR (400 MHz, $CDCl_3$) δ; 3.11 (1H, brs), 2.58-2.52 (2H, m), 2.32 (1H, dd, J = 16.0, 14.0 Hz), 2.11 (1H, brd, J = 12.1 Hz), 1.96-1.86 (2H, m), 1.64 (1H, ddd, J = 26.2, 14.0, 2.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 38.4, 39.2, 39.9, 41.7 (d, J = 23.2 Hz), 56.3 (d, J = 16.0 Hz), 66.7 (d, J = 6.5 Hz), 101.9 (d, J = 197.4 Hz), 174.9, 175.9 (d, J = 28.9 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; -89.2,

-89.7 (m). ESI-MS *m/z*: 218 (M^++H^+). FAB-MS calcd for $C_9H_{12}FNO_4$+H^+: 218.0829 (M^++H^+). Found: 218.0818.

(1*R*, 2*R*, 4*R*, 6*R*)-6-Amino-2-fluorobicyclo[2.2.1]heptane-2,6-dicarboxylic acid (+)-5

In a similar manner for the preparation of (-)-5, (+)-5 (12 mg, 69%) was obtained from (+)-11 (32 mg, 0.08 mmol) as colorless solid. dec 200 ℃. $[\alpha]_D^{24}$ +26.3 (c 0.26, H_2O).

Methyl (1*R*,2*R*,4*R*,6*R*)-6-amino-6-cyano-2-fluorobicyclo[2.2.1]heptane-2-carboxylate (+)-12

Under a hydrogen atmosphere a mixture of **9b** (80 mg, 0.2 mmol) and 10% Pd-C in MeOH (2 mL) was stirred for 16 h at rt, and then the catalyst was filtered off. The filtrate was treated with diazomethane to give (+)-12 (11 mg, 24%) after column chromatography (SiO_2, hexane : AcOEt =2 : 1). Colorless crystals. mp 93-95 ℃ (from Et_2O). $[\alpha]_D^{23}$ +32.7 (c 0.22, $CHCl_3$). IR (KBr) νcm^{-1}; 3347, 2225, 1738. ^1H NMR (400 MHz, $CDCl_3$) δ; 3.82 (3H, s), 2.75 (1H, brs), 2.48-2.35 (2H, m), 2.20 (1H, brd, *J* = 11.0 Hz), 2.15 (1H, dd, *J* = 13.2, 2.3 Hz) 1.85-1.65 (2H, m), 1.64 (1H, ddd, *J* = 26.1, 13.9, 4.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 35.8, 36.5, 41.0 (d, *J* = 23.7 Hz), 45.3, 50.0 (d, *J* = 6.0 Hz), 53.4, 55.8 (d, *J* = 15.9 Hz), 98.6 (d, *J* = 203.1 Hz), 124.9, 171.3 (d, *J* = 27.4 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; -99.0 (dd, *J* = 26.1, 17.0 Hz). EI-MS *m/z*: 212 (M^+). Anal. Calcd for $C_{10}H_{13}FN_2O_2$: C, 56.60; H, 6.17; N, 13.20. Found: C, 56.47; H, 6.17; N, 13.08.

Benzyl (1*S*, 2*S*, 4*S*)-2-fluorobicyclo[2.2.1]hept-5-ene-2-carboxylate (-)-2

After the Diels-Alder adduct **13** (*exo* only, 92% de, 1.1 g, 3.0 mmol), obtained from the reaction of (1*R*,2*S*,5*R*)-8-phenylmenthyl 2-fluoroacrylate **1b** with cyclopentadiene,[7] in EtOH (24 mL)-THF (8 mL) was treated with 3N NaOH(16 mL) for 3 d at rt, the mixture was acidified to pH 4 by the addition of 10% HCl and extracted with AcOEt. The organic extract was concentrated under reduced pressure and the residue was chromatographed (SiO_2, AcOEt) to give the carboxylic acid [422 mg, 91%, $[\alpha]_D^{24}$ -118.0 (c 0.99, $CHCl_3$)] as a colorless oil. After a mixture of the carboxylic acid (422 mg, 2.7 mmol), benzyl alcohol (0.4 mL, 3.86 mmol) and EDC (1.3 g, 6.78 mmol) in CH_2Cl_2 (10 mL) was stirred for 2 d at rt, the mixture was extracted with Et_2O after addition of H_2O. Chromatographic purification (SiO_2, hexane : AcOEt=25 : 1) gave (-)-2 (658 mg, 77%) as a colorless oil. $[\alpha]_D^{24}$ -81.5 (c 1.06, $CHCl_3$).

Benzyl (1*S*,2*S*,4*S*,6*S*)-2-fluoro-6-hydroxybicyclo[2.2.1]heptane-2-carboxylate (-)-6 and benzyl (1*S*, 2*S*, 4*S*, 5*R*)-2-fluoro-5-hydroxybicyclo[2.2.1]heptane-2-carboxylate (-)-7

In a similar manner for the preparation of racemic **6** and **7**, (-)-6 (326 mg, 46%) and (-)-7 (164 mg, 23%) were obtained from (-)-2 (658 mg). (-)-6: colorless oil. $[\alpha]_D^{26}$ -17.8 (c 0.83, $CHCl_3$). (-)-7: colorless oil. $[\alpha]_D^{26}$ -14.6 (c 0.71, $CHCl_3$).

Benzyl (1*S*, 2*S*, 4*S*)-2-fluoro-6-oxobicyclo[2.2.1]heptane-2-carboxylate (+)-3

In a similar manner for the preparation of racemic **3**, (+)-3 (282 mg, 90%) was obtained from (-)-6 (314 mg) as a colorless oil. $[\alpha]_D^{26}$ +2.6 (c 0.93, $CHCl_3$).

Benzyl (1*S*,2*S*,4*S*,6*S*)-6-cyano-2-fluoro-6-[(1*S*)-(1-phenylethyl)amino]bicyclo[2.2.1]-heptane-2-carboxylate (9a) from (+)-3

In a similar manner for the preparation of **9a** and **9b** from racemic **3**, **9a** (181 mg), along with the recovery of (+)-**3** (67 mg), was obtained from (+)-**3** (271 mg) as colorless solid. $[\alpha]_D^{28}$ -95.4 (c 0.89, $CHCl_3$).

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