

Scalable Synthesis of (+)-2-Amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid as a Potent and Selective Group II Metabotropic Glutamate Receptor Agonist

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We successfully synthesized the potent and selective group II mGluR agonist (+)-1 (MGS0008) via a process incorporating the key step of efficient fluorination of epoxide (±)-5c. This method would be adaptable to large-scale synthesis to produce (+)-1 in multi-gram quantities.

Key words group II mGluR agonist; large-scale synthesis; fluorination

L-Glutamate is the primary excitatory neurotransmitter in the mammalian central nervous system.^{1,2)} Glutamate receptors are classified as ionotropic glutamate receptors (iGluRs), which have an ion channel structure, and metabotropic glutamate receptors (mGluRs), which are G-protein-coupled receptors. mGluRs are in turn divided into three subgroups (groups I–III), a division determined by similarities in the coupling mechanisms, molecular structure, and homology of sequences and the pharmacology of the receptors.^{3–9)} Group I mGluRs (mGluR 1 and 5) activate phospholipase C, while both group II mGluRs (mGluR 2 and 3) and group III mGluRs (mGluR 4, 6, 7 and 8) inhibit adenyl cyclase.^{9–11)} Animal models and clinical trials suggest that agonists of group II mGluRs may be effective in treating a broad range of diseases and conditions, including schizophrenia,^{13–15)} anxiety,^{16–19)} and panic disorders.²⁰⁾

We have already reported that (+)-(1*S*,2*S*,3*S*,5*R*,6*S*)-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (+)-1 (MGS0008) was a potent and selective group II mGluR agonist.¹³⁾ Compound (±)-1 exhibited approximately 70-fold higher agonist activity than its diastereomer (±)-2 and (+)-1 is approximately 90-fold as active as its enantiomer (–)-1 (Fig. 1). Thus, stereo-controlled synthesis is required to prepare for (+)-1.

Previously, we reported the synthesis of (+)-1 (75 mg) from a known compound (+)-3a²¹⁾ in 4.1% yield (six steps), as shown in Chart 1.¹³⁾ Fluorination of epoxide (+)-5a with

potassium hydrogen difluoride (KF·HF) gave a key intermediate (–)-6a and an ester-exchange product (–)-7 in 18% and 28% yields, respectively. The requisite elaborate separation of (–)-6a and (–)-7 by silica gel column chromatography is unsuitable for large-scale synthesis. We used compound (±)-3a as a starting material for large-scale synthesis, because the reported route to optical pure compound (+)-3a²¹⁾ is unsuitable for large-scale preparation. Moreover, compound (–)-7, an hydroxyethyl ester, cannot be used for further reaction to (+)-1, due to low reactivity for selective hydrolysis at the C-6 position.

Therefore, we initiated efforts to modify the previous synthesis method of (+)-1 for large-scale synthesis. We tried two alternative synthesis routes of (±)-6a by eliminating a phenylsulfinyl group and investigating other esters (±)-6 to avoid ester exchange reactions. Here we report on two approaches to improving chemical yields and enabling use for scaleable synthesis of (+)-1.

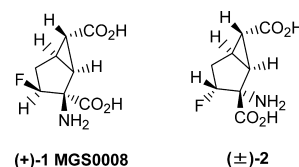
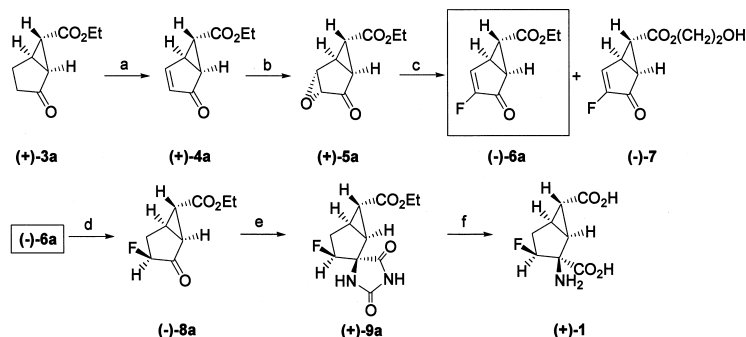


Fig. 1. Structures of (+)-1 MGS0008 and the Diastereomer (±)-2



Reagents and conditions: (a) (1) LHMS, TMSCl, THF, –68 °C to rt, 1 h; (2) Pd(OAc)₂, MeCN, 4 °C to rt, 16 h, 86%; (b) TBHP, Triton B, PhMe, 4 °C to rt, 30 min, 73%; (c) KF·HF, ethylene glycol, 130 °C, 2 h, (–)-6a: 18%, (–)-7: 28%; (d) H₂, 5% Pd/C, EtOH, rt, 12 h, 75%; (e) (NH₄)₂CO₃, KCN, EtOH, H₂O, 35 °C, 1.5 days, 61%; (f) 60% H₂SO₄ aq., 140 °C, 2 days, 79%

Chart 1

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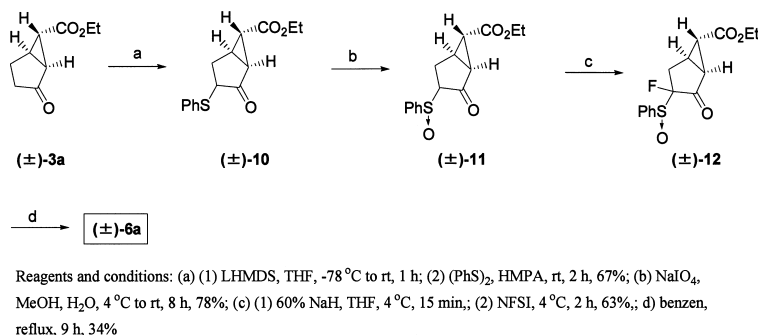


Chart 2

Results and Discussion

First, we examined an alternative synthesis method for (±)-6a to improve previous problems. A new synthesis method for (±)-6a using elimination of a phenylsulfinyl group was shown in Chart 2.

Compound (±)-11 was synthesized *via* the reaction of (±)-3a¹⁹ and diphenyl disulfide with LHMDs, followed by oxidation with sodium periodate. The hydrogen atom at C-3 position results in high acidity due to two electron withdrawing groups, phenylsulfinyl and carbonyl groups, and (±)-11 can react with electrophilic fluorination reagents. Compound (±)-12 was obtained by fluorination with *N*-fluoro-benzen-sulfonimide (NFSI)^{22,23} and the anion of (±)-11 at the C-3 position, prepared by treatment of (±)-11 with sodium hydride. Finally, eliminating the phenylsulfinyl group of (±)-12 under neutral conditions in benzene yielded vinyl fluoride (±)-6a (34% yield). Fluorination of (±)-11 with NFSI proceeded at low temperatures in comparison to the method reported with KF·HF,¹³ a nucleophilic fluorination reagent, giving (±)-6a as the sole product without elaborate separation by column chromatography.

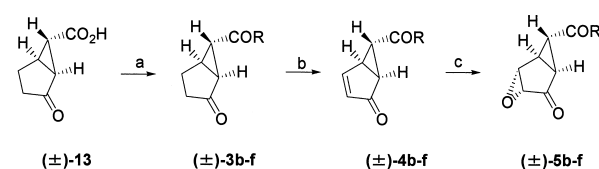
In spite of these improvements, we did not employ this method, because eliminating the phenylsulfinyl group of (±)-12 led to low yields, and phenyl sulfenylation requires hexamethylphosphoramide (HMPA), a highly toxic reagent.

To avoid ester-exchange reactions, we next investigated fluorination conditions for (±)-6a. Fluorination of (±)-5a with KH·HF in ethanol with or without 18-Crown-6 in a sealed condition at 130 °C failed. Alternatively, we attempted the fluorination of several alkyl esters (±)-5b—d and amides (±)-5e and (±)-5f, as shown in Table 1. Chart 3 shows the synthesis of (±)-5b—f from a known compound (±)-13.²⁴ Compound (±)-13 was esterified with the corresponding alkyl alcohols and amines in the presence of condensing agents. Using the reported method,¹³ we synthesized (±)-5b—f from (±)-3b—f by oxidation and epoxidation.

Fluorination of (±)-5b (isopropyl ester), an ester of the secondly alcohol, resulted in a higher yield than (±)-5a (ethyl ester), but gave (±)-7, an ester-exchange product, in 17%. The reaction of (±)-5c and (±)-5d having a bulky secondly alcohol with KF·HF gave (±)-6c and (±)-6d in 53% and 58% yields, respectively. Moreover, no ester-exchange products were detected in the reaction. Amides (±)-5e and (±)-5f were also transformed into fluoride compounds (±)-6e and (±)-6f as each sole product. Fluorination of bulky esters and amides under the reported conditions¹³ resulted in the key intermediates (±)-6c—f as the sole product. No elab-

Table 1. Fluorination of Epoxide (±)-5a—f

Entry	(±)-5	R	Yield (%)	
			(±)-6	(±)-7
1 ¹³	a	OEt	18	28
2	b	*-O-CH(CH ₃) ₂	35	17
3	c	*-O-C(CH ₃) ₂ -CH ₃	53	0
4	d	*-O-C(CH ₃) ₂ -C ₆ H ₄ -CH ₃	58	0
5	e	NHMe	58	0
6	f	NMe ₂	50	0



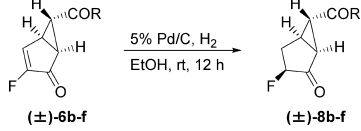
Reagents and conditions: (a) (for **b**, **c** and **d**) RH, EDC-HCl, DMAP, CHCl₃, 4 °C to rt; (for **e** and **f**) RH, EDC-HCl, HOBT, DMF, 4 °C to rt; b) (1) LHMDs, TMSCl, THF, -68 °C to rt; (2) Pd(OAc)₂, MeCN, 4 °C to rt; c) TBHP, Triton B, PhMe, 4 °C to rt; b: R = O*i*Pr, c: R = OCH(*i*Pr)₂, d: R = O-C₆H₄-CH₃, e: R = NHMe, f: R = NMe₂

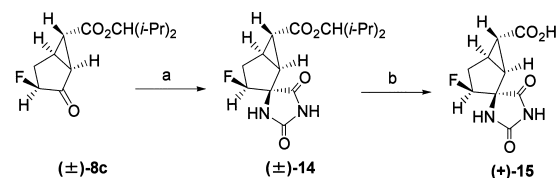
Chart 3

orate separation of a key intermediate (±)-6 and an ester-exchange product (±)-7 by column chromatography was required.

Next, we examined hydrogenation of (±)-6b—f. We previously reported that stereo selective hydrogenation of (±)-6a in the presence of 5% palladium carbon gave (±)-8a in 76% yield, due to steric hindrance with the cyclopropane ring.¹³ Hydrogenation of esters (±)-6b—d under the same conditions proceeded selectively to give (±)-8b—d in good yields, while hydrogenation of amides (±)-6e and (±)-6f failed, as shown in Table 2.

Table 2. Hydrogenation of Vinyl Fluorides ($\pm$)-6b–f

			
Entry	($\pm$)-6	R	Yield (%) ($\pm$)-8
1	b		60
2	c		86
3	d		79
4	e	NHMe	0
5	f	NMe ₂	0



Reagents and conditions: (a) (NH₄)₂CO₃, KCN, EtOH, H₂O, 36 °C, 2.5 days, 75%; b) (1) 48% HBr, 70 °C, 60 h, 82%; (2) (R)-(+)-1-phenylethylamine, acetone, H₂O, rt, 16 h, 46% (>99% ee)

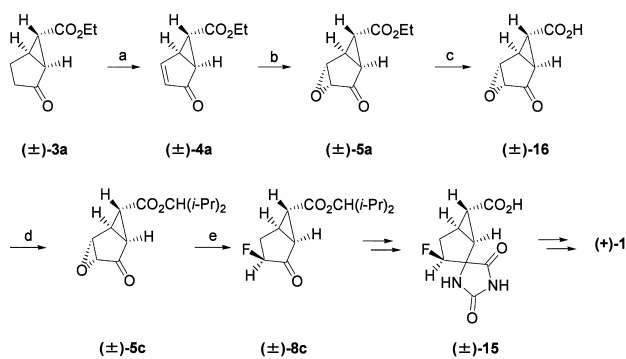
Chart 4

We adopted 2,4-dimethyl-3-pentyl ester for the large-scale synthesis of (+)-1, based on the yields for fluorination and hydrogenation, given in Tables 1 and 2.

Compound ($\pm$)-8c was allowed to react in Bucherer–Bergs conditions²⁵) to produce a hydantoin derivative ($\pm$)-14 (Chart 4). In the previous paper,¹³) we reported the efficient optical resolution of carboxylic acid ($\pm$)-15 with (R)-(+)-1-phenylethylamine in >99% ee (chemical yield 47%). In order to apply the optical resolution, we attempted selective hydrolysis of the 2,4-dimethyl-3-pentyl ester at the C-6 position of ($\pm$)-14. Compound ($\pm$)-14 was selectively hydrolyzed with 48% HBr for 60 h to give ($\pm$)-15 in 82%, and the optical resolution of the obtained carboxylic acid ($\pm$)-15 with (R)-(+)-1-phenylethylamine was successful (Chart 4). On the other hand, hydrolysis of ($\pm$)-14 using NaOH aq. or HCl aq. proceeded with 2,4-dimethyl-3-pentyl ester and hydantoin moiety to render ($\pm$)-1.

Ethyl esters, ($\pm$)-3a, ($\pm$)-4a, and ($\pm$)-5a were solid, while 2,4-dimethyl-3-pentyl ester, ($\pm$)-3c, ($\pm$)-4c, and ($\pm$)-5c were viscous oil. Therefore, we decided to change ethyl ester into 2,4-dimethyl-3-pentyl ester *via* carboxylic acid ($\pm$)-16 to purify ($\pm$)-3a, ($\pm$)-4a, and ($\pm$)-5a by recrystallization (Chart 5).

Based on the above findings, we selected the synthetic route from ($\pm$)-3a to (+)-1 (MGS0008) as shown Chart 5. We achieved the synthesis of (+)-1 (29.5 g) at a total yield of 6.7% from ($\pm$)-3a. The physical properties and spectroscopic data for (+)-1 described above identified with the previous date.



Reagents and conditions: (a) (1) LHMS, TMSCl, THF, -68 °C to rt, 1.5 h; (2) Pd(OAc)₂, MeCN, 4 °C to rt, 16 h, 90%; (b) TBHP, Triton B, PhMe, 4 °C to rt, 14 h, 92%; (c) 2 M NaOH aq., 4 °C to rt, 6 h, 92%; (d) (*i*-Pr)₂CHOH, DCC, DMAP, CHCl₃, 4 °C to rt, 2 h; (e) (1) KF·HF, ethylene glycol, 135 °C, 2.5 h; (2) 5% Pd/C, EtOH, rt, 16 h, 48% (from ($\pm$)-16)

Chart 5

Conclusions

We reported on the convenient method of synthesizing optically pure (+)-1 (MGS0008) *via* 2,4-dimethyl-3-pentyl ester ($\pm$)-8c. This synthetic route for (+)-1 did not require a fine separation of a key intermediate ($\pm$)-6 and an ester-exchange product ($\pm$)-7 with silica gel column chromatography and provided improved chemical yields compared to the previous method. Moreover, the 2,4-dimethyl-3-pentyl ester was selectively removed under hydrolysis conditions using 48% HBr, and the optical resolution of the obtained carboxylic acid with (R)-(+)-1-phenylethylamine was successful. We succeeded in producing (+)-1 in multi-gram quantities by the described method. We believe this method of synthesizing (+)-1 will help advance biological and pharmacological studies of this compound.

Experimental

Melting points were determined on a Yanaco MP-500D melting point apparatus and are uncorrected. ¹H-, ¹³C- and ¹⁹F-NMR spectra were obtained using a Varian Gemini 2000, Varian Unity Inova 300, JEOL Alpha500 or JEOL Lambda500. Chemical shifts are reported in parts per million relative to tetramethylsilane (TMS) or sodium 3-trimethylsilylpropionate-2,2,3,3-*d*₄ (TMSP) as an internal standard. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. Mass spectra (MS) were obtained on a Micromass Platform LC (ES) or Micromass GCT (EI, CI). High resolution spectra were recorded on a Micromass GCT instrument or Micromass Q-TOF2 instrument. Optical rotations were determined with a JASCO DIP-360 polarimeter and are reported at the sodium D-line (589 nm). Elemental analyses were performed on a Perkin-Elmer 2400. Silica gel (C-200, 100–200 mesh (Wako Pure Chemical)) was used for column chromatography, using the solvent systems (volume ratios) indicated below.

(1*S*,5*R*,6*S*)-3-Phenylsulfanyl-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid Ethyl Ester (($\pm$)-10) *n*-Butyl lithium (1.61 M hexane soln, 19.4 ml, 31.2 mmol) was added to the mixture of hexamethyldisilazane (HMDS) (5.00 g, 31.0 mmol) and THF (25 ml) at -78–-75 °C, and stirred for 1 h at this temperature under a nitrogen atmosphere. A solution of ($\pm$)-3a¹⁹) (5.00 g, 29.7 mmol) in THF (18 ml) was added to the mixture at -78–-73 °C. After stirring for 1 h, a solution of diphenyl disulfide (7.80 g, 35.7 mmol) in hexamethylphosphoramide (30 ml) was added, and the reaction mixture was stirred for 2 h at room temperature. Saturated aqueous NH₄Cl was added and concentrated under reduced pressure. The residue was extracted with AcOEt. The organic layer was washed with saturated aqueous NH₄Cl, saturated aqueous NaHCO₃ and saturated brine, dried (Na₂SO₄), concentrated under reduced pressure, and chromatographed on silica gel (hexane : AcOEt = 10 : 1–9 : 1) to yield ($\pm$)-10 (5.51 g, 67% yield) as a colorless oil. ¹H-NMR (200 MHz, CDCl₃) δ : 1.21–1.32 (3H, m), 1.98–2.93 (5H, m), 3.42–3.64 (1H, m), 4.10–4.22 (2H, m), 7.25–7.48 (5H, m). HR-EI-MS *m/z*: 276.0825 [Calcd for C₁₅H₁₆O₃S: 276.0820 (M⁺)].

(1*S*,5*R*,6*S*)-3-Phenylsulfanyl-2-oxobicyclo[3.1.0]hexane-6-car-

boxylic Acid Ethyl Ester ((±)-11) A solution of NaO₄ (0.938 g, 4.39 mmol) in water (4 ml) was added to a mixture of (±)-10 (1.01 g, 3.65 mmol) and MeOH (12 ml) with ice-cooling. The mixture was stirred for 1 d at room temperature. The obtained precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in AcOEt, dried (Na₂SO₄), concentrated under reduced pressure, and chromatographed on silica gel (hexane:AcOEt=3:1) to yield (±)-11 (0.830 g, 78% yield) as a colorless oil. ¹H-NMR (200 MHz, CDCl₃) δ: 1.20–1.32 (3H, m), 1.70–3.40 (6H, m), 4.06–4.22 (2H, m), 7.49–7.56 (5H, m). HR-ES-MS *m/z*: 293.0850 [Calcd for C₁₅H₁₇O₄S: 293.0848 (M⁺+1)].

(1SR,5RS,6SR)-3-Fluoro-3-phenylsulfinyl-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid Ethyl Ester ((±)-12) Under a nitrogen atmosphere, a solution of (±)-11 (0.510 g, 1.74 mmol) in THF (9.3 ml) was added to a suspension of 60% NaH in oil (77.0 mg, 1.92 mmol) in THF (9.3 ml) with ice-cooling, and the mixture was stirred for 15 min. *N*-Fluorobenzenesulfonimide (NFSI) (0.660 g, 2.09 mmol) was added to the mixture, and stirred for 2 h with ice-cooling. 1 M HCl was added to the mixture and stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure, and extracted with AcOEt. The extract was dried (Na₂SO₄), concentrated under reduced pressure, and chromatographed on silica gel (hexane:AcOEt=4:1) to yield (±)-12 (0.340 g, 63% yield) as a colorless oil. ¹H-NMR (200 MHz, CDCl₃) δ: 1.23–1.35 (3H, m), 1.97–3.32 (5H, m), 4.11–4.24 (2H, m), 7.51–7.71 (5H, m). HR-ES-MS *m/z*: 311.0752 [Calcd for C₁₅H₁₆O₄FS: 311.0753 (M⁺+1)].

(1SR,5RS,6SR)-3-Fluoro-2-oxobicyclo[3.1.0]hex-3-ene-6-carboxylic Acid Ethyl Ester ((±)-6a) A solution of (±)-12 (0.310 g, 0.999 mmol) in benzene (15.5 ml) was refluxed for 9 h, concentrated under reduced pressure, and chromatographed on silica gel (hexane:AcOEt=8:1) to yield (±)-6a (61.0 mg, 34% yield) as a colorless oil. ¹H-NMR (200 MHz, CDCl₃) δ: 1.28 (3H, t, *J*=7.0 Hz), 2.48 (1H, dt, *J*=0.66 Hz, 3.1 Hz), 2.55–2.61 (1H, m), 2.77–2.85 (1H, m), 4.17 (2H, q, *J*=7.0 Hz), 6.89–6.92 (1H, m). HR-ESI-MS *m/z*: 185.0606 [Calcd for C₉H₁₀O₃F: 185.0614 (M⁺+1)].

(1SR,5RS,6SR)-2-Oxobicyclo[3.1.0]hexane-6-carboxylic Acid 2,4-Dimethyl-3-pentyl Ester ((±)-3c) 3-Ethyl-1-[3-(dimethylamino)propyl] carbodiimide hydrochloride (EDC·HCl) (6.00 g, 31.1 mmol) was added to a mixture of (±)-13²⁴⁾ (4.00 g, 28.5 mmol), 2,4-dimethyl-3-pentanol (3.60 g, 31.0 mmol), 4-dimethylaminopyridine (350 mg, 2.86 mmol) and CHCl₃ (40 ml) with ice-cooling and the mixture was stirred for 12 h at room temperature. 1 M HCl was added to the reaction mixture and the aqueous layer was extracted twice with CHCl₃. The combined organic layer was dried (Na₂SO₄), concentrated under reduced pressure, and chromatographed on silica gel (hexane:AcOEt=10:1) to yield (±)-3c (6.69 g, 98% yield) as a colorless oil. ¹H-NMR (200 MHz, CDCl₃) δ: 0.84–0.94 (12H, m), 1.82–1.99 (2H, m), 2.03–2.36 (6H, m), 2.49–2.56 (1H, m), 4.60 (1H, t, *J*=6.2 Hz). HR-ESI-MS *m/z*: 239.1645 [Calcd for C₁₄H₂₃O₃: 239.1647 (M⁺+1)].

(1SR,5RS,6SR)-2-Oxobicyclo[3.1.0]hexane-6-carboxylic Acid Isopropyl Ester ((±)-3b) Compound (±)-3b (4.80 g, 92% yield) was obtained, as described for (±)-3c, from (±)-13 (4.00 g, 28.5 mmol) using isopropyl alcohol (1.90 g, 31.6 mmol) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ: 1.24 (3H, d, *J*=6.2 Hz), 1.25 (3H, d, *J*=6.2 Hz), 1.97–2.28 (6H, m), 2.48–2.53 (1H, m), 4.96–5.05 (1H, m). HR-ESI-MS *m/z*: 183.1026 [Calcd for C₁₀H₁₅O₃: 183.1021 (M⁺+1)].

(1SR,5RS,6SR)-2-Oxobicyclo[3.1.0]hexane-6-carboxylic Acid 2,6-Dimethylcyclohexyl Ester ((±)-3d) Compound (±)-3d (5.22 g, 97% yield) was obtained, as described for (±)-3c, from (±)-13 (3.00 g, 21.4 mmol) using 2,6-dimethylcyclohexanol (3.00 g, 23.4 mmol) as a colorless oil. ¹H-NMR (200 MHz, CDCl₃) δ: 0.80–0.92 (6H, m), 1.09–1.82 (8H, m), 2.02–2.33 (6H, m), 2.50–2.57 (1H, m), 4.27–5.04 (1H, m). HR-ES-MS *m/z*: 251.1646 [Calcd for C₁₅H₂₃O₃: 251.1647 (M⁺+1)].

(1SR,5RS,6SR)-2-Oxobicyclo[3.1.0]hexane-6-carboxylic acid methylamide ((±)-3e) EDC·HCl (7.40 g, 38.6 mmol) was added to a mixture of (±)-13 (4.50 g, 32.1 mmol), 40% methanolic methylamine (3.00 g, 38.8 mmol), 1-hydroxybenzotriazole hydrate (6.10 g, 39.8 mmol) and *N,N*-dimethylformamide (45 ml) with ice-cooling, and the mixture was stirred for 15 h at room temperature. Water and a mixture of CHCl₃ and MeOH (9:1) were added to the reaction mixture, and the aqueous layer was separated. The aqueous layer was extracted with a mixture of CHCl₃ and MeOH (9:1) four times. The combined organic layer was dried (Na₂SO₄), concentrated under reduced pressure, and chromatographed on silica gel (CHCl₃:MeOH=30:1) to yield (±)-3e (4.68 g, 96% yield) as a solid. mp 112–116 °C. ¹H-NMR (300 MHz, CDCl₃) δ: 1.79 (1H, dd, *J*=2.6, 3.4 Hz), 1.93–2.29 (5H, m), 2.50–2.55 (1H, m), 2.82 (3H, d, *J*=4.8 Hz), 6.14 (1H, s). HR-ES-MS *m/z*: 152.0704 [Calcd for C₈H₁₀NO₂: 152.0712 (M⁺+1)].

(1SR,5RS,6SR)-2-Oxobicyclo[3.1.0]hexane-6-carboxylic Acid Dimethylamide ((±)-3f) In a similar manner to the preparation of (±)-3e, (±)-3f (5.10 g, 95% yield) was obtained from (±)-13 (4.50 g, 32.1 mmol) using 50% aqueous dimethylamine (3.50 g, 38.8 mmol) as a solid. mp 49–52 °C. ¹H-NMR (200 MHz, CDCl₃) δ: 2.01–2.28 (6H, m), 2.53–2.58 (1H, m), 2.97 (3H, s), 3.17 (3H, s). HR-ESI-MS *m/z*: 168.1017 [Calcd for C₉H₁₄NO₂: 168.1025 (M⁺+1)].

(1SR,5RS,6SR)-2-Oxobicyclo[3.1.0]hex-3-ene-6-carboxylic Acid Ethyl Ester ((±)-4a) *n*-Butyl lithium (2.46 M hexane soln, 725 ml, 1.78 mol) was added to a mixture of HMDS (288 g, 1.78 mol) and THF (750 ml) at –68––65 °C, and the mixture was stirred for 1 h under a nitrogen atmosphere. A solution of (±)-3a¹⁹⁾ (250 g, 1.49 mol) in THF (500 ml) was added to the mixture at –68––63 °C, and the mixture was stirred for 1 h. TMSCl (282 ml, 2.23 mol) was added, and the reaction mixture was stirred for 1.5 h at room temperature. The obtained inorganic salt was filtered off and the filtrate was concentrated under reduced pressure. Hexane was added to the residue, the resulting inorganic salts were filtered off, and the filtrate was concentrated under reduced pressure.

Pd(OAc)₂ (367 g, 1.63 mol) was added to a solution of the residue in MeCN (1780 ml) with ice-cooling maintained below 24 °C, and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through Celite® pad and the filtrate was concentrated under reduced pressure. The Celite® pad was washed with AcOEt (1800 ml). The combined filtrate was washed with water and saturated brine. The organic layer was dried (Na₂SO₄), concentrated under reduced pressure, short-chromatographed on silica gel (750 ml, hexane:AcOEt=1:1), and recrystallized from isopropyl ether to yield (±)-4a (222 g, 90% yield) as a yellow solid. mp 79–82 °C. ¹H-NMR (200 MHz, CDCl₃) δ: 1.27 (3H, t, *J*=7.0 Hz), 2.27 (1H, t, *J*=2.6 Hz), 2.60–2.65 (1H, m), 2.96 (1H, dt, *J*=2.6, 5.0 Hz), 4.15 (3H, q, *J*=7.0 Hz), 5.74 (1H, d, *J*=5.7 Hz), 7.61 (1H, dd, *J*=2.6, 5.7 Hz). ¹³C-NMR (126 MHz, CDCl₃) δ: 14.1, 28.9, 30.0, 45.8, 61.3, 129.6, 159.6, 167.9, 203.2. IR (KBr) cm^{–1}: 1718, 1697, 1566, 684. CI-MS *m/z*: 167 (M⁺+1). *Anal.* Calcd for C₉H₁₀O₃: C, 65.05; H, 6.07. Found C, 65.01; H, 6.04.

(1SR,5RS,6SR)-2-Oxobicyclo[3.1.0]hex-3-ene-6-carboxylic Acid Isopropyl Ester ((±)-4b) Compound (±)-3b (4.60 g, 25.2 mol) was reacted in a similar manner to preparation of (±)-4a from (±)-3a and then purified on silica gel chromatography to yield (±)-4b (2.42 g, 79% yield) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ: 1.23 (3H, d, *J*=6.2 Hz), 1.24 (3H, d, *J*=6.2 Hz), 2.24 (1H, t, *J*=2.8 Hz), 2.60–2.63 (1H, m), 2.93–2.96 (1H, m), 4.95–5.03 (1H, m), 5.73 (1H, d, *J*=5.7 Hz), 7.61 (1H, dd, *J*=2.6, 5.7 Hz). HR-ESI-MS *m/z*: 181.0877 [Calcd for C₁₀H₁₃O₃: 181.0865 (M⁺+1)].

(1SR,5RS,6SR)-2-Oxobicyclo[3.1.0]hex-3-ene-6-carboxylic Acid 2,4-Dimethyl-3-pentyl Ester ((±)-4c) Compound (±)-3c (6.53 g, 27.4 mol) was reacted in a similar manner to preparation of (±)-4a from (±)-3a and then purified on silica gel chromatography to yield (±)-4c (5.18 g, 80% yield) as a colorless oil. ¹H-NMR (200 MHz, CDCl₃) δ: 0.84–0.90 (12H, m), 1.82–1.96 (2H, m), 2.31 (1H, d, *J*=2.6 Hz), 2.62–2.66 (1H, m), 2.96 (1H, dt, *J*=2.6, 5.1 Hz), 4.58 (1H, t, *J*=6.2 Hz), 5.75 (1H, d, *J*=5.7 Hz), 7.64 (1H, dd, *J*=2.6, 5.7 Hz). HR-ESI-MS *m/z*: 237.1503 [Calcd for C₁₄H₂₁O₃: 237.1491 (M⁺+1)].

(1SR,5RS,6SR)-2-Oxobicyclo[3.1.0]hex-3-ene-6-carboxylic Acid 2,4-Dimethylcyclohexyl Ester ((±)-4d) Compound (±)-3d (5.20 g, 20.8 mol) was reacted in a similar manner to preparation of (±)-4a from (±)-3a and then purified on silica gel chromatography to yield (±)-4d (3.92 g, 76% yield) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ: 0.78–0.95 (6H, m), 0.98–2.59 (8H, m), 2.28–2.35 (1H, m), 2.60–2.68 (1H, m), 2.93–3.00 (1H, m), 4.25–5.05 (1H, m), 5.70–5.78 (1H, m), 7.60–7.66 (1H, m). HR-ES-MS *m/z*: 271.1304 [Calcd for C₁₅H₂₀O₃Na: 271.1310 (M⁺+Na)].

(1SR,5RS,6SR)-2-Oxobicyclo[3.1.0]hex-3-ene-6-carboxylic Acid Methylamide ((±)-4e) Compound (±)-3e (4.51 g, 29.4 mol) was reacted in a similar manner to preparation of (±)-4a from (±)-3a and then purified on silica gel chromatography to yield (±)-4e (1.57 g, 37% yield) as a solid. mp 125–129 °C. ¹H-NMR (200 MHz, CDCl₃) δ: 2.04 (1H, t, *J*=2.6 Hz), 2.60–2.64 (1H, m), 2.82 (3H, d, *J*=4.8 Hz), 2.97–3.02 (1H, m), 5.71 (1H, d, *J*=5.5 Hz), 5.96 (1H, s), 7.62 (1H, dd, *J*=2.6, 5.5 Hz). HR-ES-MS *m/z*: 150.0551 [Calcd for C₈H₈NO₂: 150.0555 (M⁺+1)].

(1SR,5RS,6SR)-2-Oxobicyclo[3.1.0]hex-3-ene-6-carboxylic Acid Dimethylamide ((±)-4f) Compound (±)-3f (3.90 g, 23.3 mol) was reacted in a similar manner to preparation of (±)-4a from (±)-3a and then purified on silica gel chromatography to yield (±)-4f (1.57 g, 37% yield) as a colorless oil. ¹H-NMR (200 MHz, CDCl₃) δ: 2.40 (1H, t, *J*=2.9 Hz), 2.58–2.63 (1H, m), 2.95 (3H, s), 2.97–3.08 (1H, m), 3.14 (3H, s), 5.75 (1H, d, *J*=5.7 Hz), 7.64 (1H, dd, *J*=2.6, 5.7 Hz). HR-ESI-MS *m/z*: 166.0856 [Calcd

for $C_9H_{12}NO_2$: 166.0868 ($M^+ + 1$).

(1SR,3RS,4RS,5RS,6SR)-3,4-Epoxy-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid Ethyl Ester ((±)-5a) Aqueous 70% *tert*-butyl hydroperoxide (TBHP) (289 g, 2.25 mol) and 40% benzyltrimethylammonium hydroxide (Triton B) in water (16.8 g, 40.2 mmol) was added to a solution of (±)-**4a** (220 g, 1.32 mol) in toluene (1320 ml) with ice-cooling, and the reaction mixture was stirred for 14 h at room temperature. 2 M aqueous $Na_2S_2O_3$ (125 ml) was added and the mixture was stirred for 2 h. The resulting precipitate was filtrated and washed with toluene (80 ml) and water (650 ml) to yield (±)-**5a** (182 g, 75% yield) as a colorless solid.

The organic layer of filtrate was separated. The aqueous layer was extracted with AcOEt. The combined organic layer was washed with saturated brine, dried (Na_2SO_4), concentrated under reduced pressure to yield solid (80 g). A suspension of the obtained solid in isopropyl ether (240 ml) was stirred for 2 h at room temperature then was stirred for 2 h with ice-cooling. The solid was filtrated to give (±)-**5a** (41 g, 17% yield) as a colorless solid. mp 100–105 °C. 1H -NMR (200 MHz, $CDCl_3$) δ : 1.28 (3H, t, $J=7.0$ Hz), 2.09 (1H, t, $J=3.1$ Hz), 2.21 (1H, ddt, $J=1.1, 2.4, 5.3$ Hz), 2.93–2.98 (1H, m), 3.25 (1H, dt, $J=1.1, 2.4$ Hz), 4.00 (1H, t, $J=2.4$ Hz), 4.17 (2H, q, $J=7.0$ Hz). ^{13}C -NMR (126 MHz, $CDCl_3$) δ : 14.1, 28.9, 29.8, 30.4, 50.5, 56.3, 61.7, 168.1, 200.5. IR (KBr) cm^{-1} : 1737, 1721, 902. CI-MS m/z : 183 ($M^+ + 1$). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.26; H, 5.47.

(1SR,3RS,4RS,5RS,6SR)-3,4-Epoxy-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid Isopropyl Ester ((±)-5b) Compound (±)-**4b** (2.80 g, 15.5 mmol) was reacted in a similar manner to preparation of (±)-**5a** from (±)-**4a** and then purified on silica gel chromatography to yield (±)-**5b** (2.42 g, 79% yield) as a colorless solid. mp 44–46 °C. 1H -NMR (300 MHz, $CDCl_3$) δ : 1.24 (3H, d, $J=6.2$ Hz), 1.25 (3H, d, $J=6.2$ Hz), 2.06 (1H, t, $J=3.1$ Hz), 2.18–2.23 (1H, m), 2.93–2.96 (1H, m), 3.23–3.25 (1H, m), 4.00 (1H, t, $J=2.4$ Hz), 4.94–5.07 (1H, m). HR-CI-MS m/z : 197.0802 [Calcd for $C_{10}H_{13}O_4$: 197.0814 ($M^+ + 1$)].

(1SR,3RS,4RS,5RS,6SR)-3,4-Epoxy-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid 2,4-Dimethyl-3-pentyl Ester ((±)-5c) Compound (±)-**4c** (4.08 g, 17.3 mmol) was reacted in a similar manner to preparation of (±)-**5a** from (±)-**4a** and then purified on silica gel chromatography to yield (±)-**5c** (3.46 g, 80% yield) as a colorless oil. 1H -NMR (200 MHz, $CDCl_3$) δ : 0.83–0.90 (12H, m), 1.86–1.96 (2H, m), 2.14 (1H, t, $J=3.1$ Hz), 2.19–2.25 (1H, m), 2.94–2.99 (1H, m), 3.24–3.26 (1H, m), 4.03 (1H, t, $J=2.3$ Hz), 4.60 (1H, t, $J=6.2$ Hz). ^{13}C -NMR (126 MHz, $CDCl_3$) δ : 17.2, 19.5, 28.7, 29.3, 29.9, 30.3, 50.6, 56.4, 84.5, 168.1, 200.5. IR (neat) cm^{-1} : 2968, 1745, 1726, 895. HR-CI-MS m/z : 253.1429 [Calcd for $C_{14}H_{21}O_4$: 253.1440 ($M^+ + 1$)].

(1SR,3RS,4RS,5RS,6SR)-3,4-Epoxy-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid 2,4-Dimethylcyclohexyl Ester ((±)-5d) Compound (±)-**4d** (3.80 g, 15.3 mmol) was reacted in a similar manner to preparation of (±)-**5a** from (±)-**4a** and then purified on silica gel chromatography to yield (±)-**5d** (3.46 g, 80% yield) as a colorless oil. 1H -NMR (200 MHz, $CDCl_3$) δ : 0.80–0.92 (6H, m), 1.03–2.60 (8H, m), 2.10–2.27 (1H, m), 2.95–2.99 (1H, m), 3.25–3.27 (1H, m), 4.02–4.05 (1H, m), 4.27–5.04 (1H, m). HR-CI-MS m/z : 265.1447 [Calcd for $C_{15}H_{21}O_4$: 265.1440 ($M^+ + 1$)].

(1SR,3RS,4RS,5RS,6SR)-3,4-Epoxy-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid Methylamide ((±)-5e) Compound (±)-**4e** (1.50 g, 9.92 mmol) was reacted in a similar manner to preparation of (±)-**5a** from (±)-**4a** and then purified on silica gel chromatography to yield (±)-**5e** (1.04 g, 63% yield) as a solid. mp 156–159 °C. 1H -NMR (200 MHz, $CDCl_3$) δ : 1.83 (1H, t, $J=3.0$ Hz), 2.18 (1H, ddt, $J=1.1, 2.6, 5.2$ Hz), 2.84 (3H, d, $J=4.8$ Hz), 2.97–3.02 (1H, m), 3.22 (1H, dt, $J=1.1, 2.4$ Hz), 3.98 (1H, t, $J=2.4$ Hz), 5.79 (1H, s). HR-ES-MS m/z : 166.0494 [Calcd for $C_8H_8NO_3$: 166.0504 ($M^+ - 1$)].

(1SR,3RS,4RS,5RS,6SR)-3,4-Epoxy-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid Dimethylamide ((±)-5f) Compound (±)-**4f** (2.71 g, 16.4 mmol) was reacted in a similar manner to preparation of (±)-**5a** from (±)-**4a** and then purified on silica gel chromatography to yield (±)-**5f** (1.88 g, 63% yield) as a solid. mp 112–118 °C. 1H -NMR (300 MHz, $CDCl_3$) δ : 2.13–2.16 (1H, m), 2.24 (1H, t, $J=3.1$ Hz), 2.97 (3H, s), 3.04–3.07 (1H, m), 3.15 (3H, s), 3.24–3.26 (1H, m), 3.99 (1H, t, $J=2.3$ Hz). HR-EI-MS m/z : 181.0732 [Calcd for $C_9H_{11}NO_3$: 181.0739 (M^+)].

(1SR,5RS,6SR)-3-Fluoro-2-oxobicyclo[3.1.0]hex-3-ene-6-carboxylic Acid Isopropyl Ester ((±)-6b) and **(1SR,5RS,6SR)-3-Fluoro-2-oxobicyclo[3.1.0]hex-3-ene-6-carboxylic Acid 2-Hydroxyethyl Ester ((±)-7)** A mixture of (±)-**5b** (2.85 g, 14.5 mmol) and $KF \cdot HF$ (11.3 g, 145 mmol) in ethylene glycol (42 ml) was stirred at 130 °C for 2 h under a nitrogen atmosphere. The reaction mixture was poured onto ice and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$), concentrated under reduced pressure,

and chromatographed on silica gel (hexane:AcOEt=6:1–1:1–1:2) to yield (±)-**6b** (1.01 g, 35% yield) and (±)-**7** (490 mg, 17% yield) as colorless oil.

(±)-**6b**: 1H -NMR (300 MHz, $CDCl_3$) δ : 1.24 (3H, d, $J=6.2$ Hz), 1.26 (3H, d, $J=6.2$ Hz), 2.45 (1H, t, $J=2.8$ Hz), 2.55–2.59 (1H, m), 2.77–2.82 (1H, m), 4.96–5.04 (1H, m), 6.89–6.91 (1H, m). HR-CI-MS m/z : 199.0785 [Calcd for $C_{10}H_{12}O_3F$: 199.0770 ($M^+ - 1$)].

(±)-**7**: 1H -NMR (200 MHz, $CDCl_3$) δ : 1.72–2.00 (1H, s), 2.52–2.64 (2H, m), 2.80–2.88 (1H, m), 3.81–3.88 (2H, m), 4.24–4.28 (2H, m), 6.90–6.93 (1H, m). HR-CI-MS m/z : 201.0588 [Calcd for $C_9H_{10}O_4F$: 201.0563 ($M^+ - 1$)].

(1SR,5RS,6SR)-3-Fluoro-2-oxobicyclo[3.1.0]hex-3-ene-6-carboxylic Acid 2,4-Dimethyl-3-pentyl Ester ((±)-6c) Compound (±)-**6c** (570 mg, 53% yield) was obtained, as described for (±)-**6b**, from (±)-**5c** (1.06 g, 4.20 mmol) as a colorless oil. 1H -NMR (200 MHz, $CDCl_3$) δ : 0.84–0.90 (12H, m), 1.83–1.96 (2H, m), 2.51–2.62 (2H, m), 2.77–2.85 (1H, m), 4.59 (1H, t, $J=6.2$ Hz), 6.92–6.94 (1H, m). HR-ES-MS m/z : 253.1230 [Calcd for $C_{14}H_{18}O_3F$: 253.1240 ($M^+ - 1$)].

(1SR,5RS,6SR)-3-Fluoro-2-oxobicyclo[3.1.0]hex-3-ene-6-carboxylic Acid 2,4-Dimethylcyclohexyl Ester ((±)-6d) Compound (±)-**6d** (453 mg, 58% yield) was obtained, as described for (±)-**6b**, from (±)-**5d** (780 mg, 2.95 mmol) as a colorless oil. 1H -NMR (300 MHz, $CDCl_3$) δ : 0.81–0.92 (6H, m), 1.05–2.31 (8H, m), 2.51–2.64 (2H, m), 2.79–2.84 (1H, m), 4.02–5.03 (1H, m), 6.91–6.94 (1H, m). HR-CI-MS m/z : 267.1380 [Calcd for $C_{15}H_{20}O_3F$: 267.1396 ($M^+ + 1$)].

(1SR,5RS,6SR)-3-Fluoro-2-oxobicyclo[3.1.0]hex-3-ene-6-carboxylic Acid Methylamide ((±)-6e) Compound (±)-**6e** (573 mg, 58% yield) was obtained, as described for (±)-**6b**, from (±)-**5e** (980 mg, 5.86 mmol) as a colorless oil. 1H -NMR (200 MHz, $CDCl_3$) δ : 2.24 (1H, t, $J=2.9$ Hz), 2.56–2.63 (1H, m), 2.83 (3H, d, $J=5.1$ Hz), 2.85–2.89 (1H, m), 5.85 (1H, s), 6.90 (1H, dt, $J=1.3, 2.9$ Hz). HR-ES-MS m/z : 168.0459 [Calcd for $C_8H_7NO_3F$: 168.0461 ($M^+ - 1$)].

(1SR,5RS,6SR)-3-Fluoro-2-oxobicyclo[3.1.0]hex-3-ene-6-carboxylic Acid Dimethylamide ((±)-6f) Compound (±)-**6f** (840 mg, 50% yield) was obtained, as described for (±)-**6b**, from (±)-**5f** (1.68 g, 9.27 mmol) as a colorless oil. 1H -NMR (200 MHz, $CDCl_3$) δ : 2.56–2.64 (2H, m), 2.88–2.94 (1H, m), 2.96 (3H, s), 3.15 (3H, s), 6.92 (1H, dt, $J=1.3, 2.9$ Hz). HR-ES-MS m/z : 182.0603 [Calcd for $C_9H_9NO_3F$: 182.0617 ($M^+ - 1$)].

(1SR,3SR,5RS,6SR)-3-Fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid Isopropyl Ester ((±)-8b) A mixture of (±)-**6b** (660 mg, 3.33 mmol) and 5% Pd-C (66.0 mg) in EtOH (6.0 ml) was stirred under a hydrogen atmosphere at room temperature for 12 h. Filtration through Celite® pad, concentration under reduced pressure, and chromatographed on silica gel (hexane:AcOEt=6:1) yielded (±)-**8b** (398 mg, 60% yield) as a colorless oil. 1H -NMR (300 MHz, $CDCl_3$) δ : 1.25 (3H, d, $J=6.2$ Hz), 1.26 (3H, d, $J=6.2$ Hz), 1.96–2.64 (5H, m), 4.52 (1H, dt, $J=7.6, 50$ Hz), 5.02 (1H, m). HR-ES-MS m/z : 199.0743 [Calcd for $C_{10}H_{12}O_3F$: 199.0770 ($M^+ - 1$)].

(1SR,3SR,5RS,6SR)-3-Fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid 2,4-Dimethyl-3-pentyl Ester ((±)-8c) Compound (±)-**8c** (469 mg, 86% yield) was obtained, as described for (±)-**8b**, from (±)-**6c** (540 mg, 2.12 mmol) as a colorless oil. 1H -NMR (200 MHz, $CDCl_3$) δ : 0.85–0.91 (12H, m), 1.84–2.05 (2H, m), 2.19–2.60 (5H, m), 4.38–4.67 (2H, m). ^{13}C -NMR (126 MHz, $CDCl_3$) δ : 17.3 (s), 19.6 (s), 26.2 (s), 27.9 (s), 29.5 (s), 30.7 (d, $J=21.2$ Hz), 34.0 (s), 84.3 (s), 88.7 (d, $J=182.0$ Hz), 169.6 (s), 204.2 (d, $J=12.5$ Hz). ^{19}F -NMR (470 MHz, $DMSO-d_6$) δ : –174.0. IR (neat) cm^{-1} : 2968, 1750, 1728. HR-CI-MS m/z : 257.1556 [Calcd for $C_{14}H_{22}O_3F$: 257.1553 ($M^+ + 1$)].

(1SR,3SR,5RS,6SR)-3-Fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid 2,4-Dimethylcyclohexyl Ester ((±)-8d) Compound (±)-**8d** (890 mg, 79% yield) was obtained, as described for (±)-**8b**, from (±)-**6d** (1.11 g, 4.17 mmol) as a colorless oil. 1H -NMR (300 MHz, $CDCl_3$) δ : 0.80–0.94 (6H, m), 1.02–2.66 (13H, m), 4.00–5.05 (2H, m). HR-ES-MS m/z : 267.1384 [Calcd for $C_{15}H_{20}O_3F$: 267.1396 ($M^+ - 1$)].

(1SR,2SR,3SR,5RS,6SR)-2-Spiro-5'-hydantoin-3-fluorobicyclo[3.1.0]hexane-6-carboxylic Acid 2,4-Dimethyl-3-pentyl Ester ((±)-14) A mixture of (±)-**8c** (339 g, 1.32 mol), ammonium carbonate (318 g, 3.31 mol), and potassium cyanide (94.6 g, 1.45 mol) in a mixture of EtOH (850 ml) and water (570 ml) was stirred at 36 °C for 2.5 d. Water (1130 ml) was added to the reaction mixture and the mixture was stirred for 3 h with ice-cooling. The resulting precipitate was filtered and the precipitate was washed with a mixture of EtOH (300 ml) and water (600 ml) and then water (1250 ml) to yield (±)-**14** (303 g, 70% yield). 2 M NaOH (200 ml) was added to the combined filtrate, and the mixture was concentrated under reduced pressure for removing EtOH. The residue was extracted with AcOEt (1000 ml, 500 ml).

The combined extract was washed with saturated brine (500 ml), dried (Na_2SO_4), concentrated under reduced pressure, and recrystallized from isopropanol (240 ml) to yield ($\pm$)-**14** (19.8 g, 5% yield) as a colorless solid. mp 218–220 °C. $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 0.86 (6H, d, $J=6.8$ Hz), 0.88 (6H, d, $J=6.8$ Hz), 1.82–1.99 (2H, m), 2.09 (1H, t, $J=2.9$ Hz), 2.20–2.78 (4H, m), 4.60 (1H, t, $J=6.2$ Hz), 4.74 (1H, dd, $J=5.5$, 53 Hz), 5.62 (1H, s), 7.59 (1H, s). $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ : 17.3 (s), 19.6 (s), 23.3 (s), 25.3 (s), 29.5 (s), 31.7 (s), 34.6 (d, $J=18.7$ Hz), 72.5 (d, $J=17.5$ Hz), 83.6 (s), 93.4 (d, $J=188.2$ Hz), 155.4 (s), 171.2 (s), 172.4 (d, $J=7.5$ Hz). $^{19}\text{F-NMR}$ (470 MHz, CDCl_3) δ : -176.2. IR (KBr) cm^{-1} : 3202, 2968, 1774, 1737, 1718. ES-MS m/z : 325 ($\text{M}^+ - 1$). Anal. Calcd for $\text{C}_{16}\text{H}_{23}\text{FN}_2\text{O}_4$: C, 58.88; H, 7.10; N, 8.58; F, 5.82. Found: C, 59.19; H, 7.14; N, 8.28; F, 5.54.

(1SR,2SR,3SR,5SR,6SR)-2-Spiro-5'-hydantoin-3-fluorobicyclo[3.1.0]hexane-6-carboxylic Acid (($\pm$)-15**)** A suspension of ($\pm$)-**14** (223 g, 0.683 mol) in 48% HBr (1500 ml) was stirred for 60 h at 70 °C under a nitrogen atmosphere. After cooling, hexane (750 ml) was added to the mixture. The mixture was stirred for 5 h with ice-cooling, and the resulting precipitate was filtered and washed with hexane (300 ml) and cold water (260 ml) to yield ($\pm$)-**15** (128 g, 82% yield) as a yellow solid. mp 319 °C (decomposed). $^1\text{H-NMR}$ (200 MHz, $\text{DMSO}-d_6$) δ : 1.85–2.44 (5H, m), 4.80 (1H, dd, $J=5.3$, 52 Hz), 8.44 (1H, m), 10.88 (1H, s), 12.30 (1H, s). $^{13}\text{C-NMR}$ (126 MHz, $\text{DMSO}-d_6$) δ : 23.3 (s), 25.3 (s), 31.9 (s), 34.7 (d, $J=18.7$ Hz), 72.1 (d, $J=16.2$ Hz), 93.7 (d, $J=185.7$ Hz), 156.9 (s), 173.2 (s), 174.6 (d, $J=8.7$ Hz). $^{19}\text{F-NMR}$ (470 MHz, $\text{DMSO}-d_6$) δ : -174.5. IR (KBr) cm^{-1} : 3264, 3070, 1781, 1735, 1689. ES-MS m/z : 227 ($\text{M}^+ - 1$). Anal. Calcd for $\text{C}_8\text{H}_9\text{FN}_2\text{O}_4$: C, 47.37; H, 3.98; N, 12.28; F, 8.33. Found: C, 47.51; H, 4.01; N, 12.01; F, 8.18.

(1SR,3RS,4RS,5RS,6SR)-3,4-Epoxy-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid (($\pm$)-16**)** A mixture of ($\pm$)-**5a** (370 g, 2.03 mol) and 2 M NaOH (1067 ml, 2.13 mol) was stirred for 15 min with ice-cooling and for 5.5 h at room temperature. A solution of KHSO_4 (348 g, 2.56 mol) in water (649 ml) was added to the mixture with ice-cooling. AcOEt (600 ml) was added to the mixture, and the resulting inorganic precipitate was filtered off and washed with AcOEt (600 ml). The aqueous layer of the filtrate was extracted with AcOEt (1000 ml, 3 times). The combined extract was dried (Na_2SO_4), concentrated under reduced pressure to yield solid. A mixture of the solid and IPE (940 ml) was refluxed for 0.5 h and stirred for 12 h at room temperature. The solid was filtered to yield ($\pm$)-**16** (288 g, 92%) as a colorless solid. mp 121–123 °C. $^1\text{H-NMR}$ (200 MHz, $\text{DMSO}-d_6$) δ : 2.02–2.07 (1H, m), 2.39 (1H, t, $J=3.1$ Hz), 2.88–2.93 (1H, m), 3.37 (1H, dt, $J=1.2$, 2.4 Hz), 4.18 (1H, t, $J=2.4$ Hz), 12.9 (1H, s). $^{13}\text{C-NMR}$ (126 MHz, $\text{DMSO}-d_6$) δ : 28.5, 29.5, 30.6, 50.6, 56.4, 169.8, 201.8. IR (KBr) cm^{-1} : 3077, 1744, 1702, 896. EI-MS m/z : 154 (M^+). Anal. Calcd for $\text{C}_7\text{H}_6\text{O}_4$: C, 54.55; H, 3.92. Found: C, 54.30; H, 3.95.

(1SR,3RS,4RS,5RS,6SR)-3,4-Epoxy-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid 2,4-Dimethyl-3-pentyl Ester (($\pm$)-5c**)** A solution of dicyclohexylcarbodiimide (DCC) (380 g, 1.84 mol) in CHCl_3 (330 ml) was added to a mixture of ($\pm$)-**16** (258 g, 1.67 mol), 2,4-dimethyl-3-pentanol (234 g, 2.01 mol), dimethylaminopyridine (20.5 g, 167 mol) and CHCl_3 (960 ml) with ice-cooling. The reaction mixture was stirred for 2 h at room temperature. AcOH (11.5 ml, 200 mmol) was added to the reaction mixture with ice-cooling, and the mixture was stirred for 2.5 h at room temperature. Hexane (1500 ml) was added to the mixture, and the mixture was stirred for 15 h at room temperature. The precipitate was filtered off and washed with hexane:AcOEt (5:1, 2000 ml). The combined filtrate was concentrated under reduced pressure. The mixture of the residue and hexane (850 ml) was stirred for 1 h at room temperature and the resulting precipitate was filtered off. The filtrate was concentrated under reduced pressure. Toluene (2100 ml) and water (525 ml) were added to the residue, and the organic layer was separated. The organic layer was washed with 0.5 M HCl (500 ml), saturated aqueous NaHCO_3 (500 ml), dried (Na_2SO_4), and concentrated under reduced pressure. Hexane (1200 ml) was added to the residue, and the resulting precipitate was filtered off. The filtrate was concentrated under reduced pressure to yield crude ($\pm$)-**5c** (438 g) as a yellow oil. The residue was used for next step without further purification.

(1SR,5RS,6SR)-3-Fluoro-2-oxobicyclo[3.1.0]hex-3-ene-6-carboxylic Acid 2,4-Dimethyl-3-pentyl Ester (($\pm$)-6c**)** A suspension of ($\pm$)-**5c** (224 g) and $\text{KF}\cdot\text{HF}$ (665 g, 8.52 mol) in ethylene glycol (1070 ml) was stirred for 2.5 h at 131–135 °C under a nitrogen atmosphere. The reaction mixture was immediately poured onto ice (1100 g) and extracted AcOEt (1000 ml, 250 ml, 2 times). The combined extract was washed with water (400 ml, 2 times) and saturated brine (400 ml), dried (Na_2SO_4), and concentrated under reduced pressure to yield crude ($\pm$)-**6c** as a dark brown oil. The residue was used for next step without further purification.

(1SR,3SR,5RS,6SR)-3-Fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid 2,4-Dimethyl-3-pentyl Ester (($\pm$)-8c**)** A suspension of ($\pm$)-**6c** and 5% Pd/C (13.0 g) in EtOH (700 ml) was stirred under a hydrogen atmosphere for 16 h at room temperature. The mixture was filtered through Celite[®] pad and filtrate was concentrated under reduced pressure. The residue was chromatographed (4000 ml, hexane:AcOEt = 20:1–18:1) to yield ($\pm$)-**8c** (106 g, 48% yield (from ($\pm$)-**16**)) as a yellow oil.

(1S,2S,3S,5R,6S)-2-Spiro-5'-hydantoin-3-fluorobicyclo[3.1.0]hexane-6-carboxylic Acid ((+)-15**)** After (*R*)-(+)-1-phenylethylamine (95.6 g, 0.789 mol) was added to the mixture of ($\pm$)-**15** (180 g, 0.789 mol), acetone (1600 ml) and water (1000 ml) at 55 °C, the mixture was left to stand at room temperature for 16 h. The resulting crystal was filtered and washed with acetone (500 ml) to yield (*R*)-(+)-1-phenylethylamine salt of (+)-**15** (126 g, 46% yield).

The mixture of (*R*)-(+)-1-phenylethylamine salt (125 g, 0.358 mol) and water (860 ml) was adjusted to pH 1.0 with 1 M HCl, and the mixture was stirred at room temperature for 15 h. The resulting solid was collected by filtration and washed with water (60 ml) to yield (+)-**15** (71.3 g, 87% yield). mp 330 °C (decomposed). $^1\text{H-NMR}$ (200 MHz, $\text{DMSO}-d_6$) δ : 1.85–2.44 (5H, m), 4.80 (1H, dd, $J=5.3$, 52 Hz), 8.44 (1H, m), 10.88 (1H, s), 12.30 (1H, s). $^{13}\text{C-NMR}$ (126 MHz, $\text{DMSO}-d_6$) δ : 23.3 (s), 25.3 (s), 31.9 (s), 34.7 (d, $J=18.7$ Hz), 72.1 (d, $J=16.2$ Hz), 93.7 (d, $J=185.7$ Hz), 156.9 (s), 173.2 (s), 174.6 (d, $J=8.7$ Hz). $^{19}\text{F-NMR}$ (470 MHz, $\text{DMSO}-d_6$) δ : -174.5. IR (KBr) cm^{-1} : 3264, 3070, 1781, 1735, 1689. ES-MS m/z : 227 ($\text{M}^+ - 1$). Anal. Calcd for $\text{C}_8\text{H}_9\text{FN}_2\text{O}_4$: C, 47.37; H, 3.98; N, 12.28; F, 8.33. Found: C, 47.39; H, 3.94; N, 12.28; F, 8.37. $[\alpha]_D^{25} + 36.8^\circ$ ($c=0.20$, MeOH).

(1S,2S,3S,5R,6S)-2-Amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid ((+)-1**, MGS0008)** A mixture of (+)-**15** (45.0 g, 0.197 mol) and 60% H_2SO_4 (495 ml) was stirred at 145 °C for 3.5 d. After cooling, the reaction mixture was adjusted to pH 8 with 5 M NaOH. The mixture was chromatographed on AG1-X8 anion exchange resin (Bio-Rad) (OH^- form) (6300 ml) [water 9000 ml, a mixture of THF and water (1:1) 4000 ml, water 9000 ml and then 2 M aqueous AcOH 8800 ml].

The elution of 2 M aqueous AcOH was concentrated under reduced pressure to yield crude (+)-**1** (38.9 g). The crude product was dissolved in hot water (292 ml) and filtered through Celite[®] pad. The filtrate was concentrated (*ca.* 75 ml) and left to stand for 16 h at 10 °C. The resulting precipitate was filtrated and washed with cold water (25 ml) to yield (+)-**1** (29.5 g, 74% yield) as a colorless solid. mp 234 °C (decomposed). $^1\text{H-NMR}$ (300 MHz, D_2O) δ : 2.02–2.04 (1H, m), 2.23–2.04 (3H, m), 2.56–2.78 (1H, m), 5.06 (1H, dd, $J=5.8$, 53 Hz). $^{13}\text{C-NMR}$ (126 MHz, D_2O) δ : 24.2 (s), 27.6 (s), 32.8 (s), 35.4 (d, $J=18.7$ Hz), 69.3 (d, $J=13.7$ Hz), 95.1 (d, $J=184.5$ Hz), 171.3 (d, $J=6.2$ Hz), 175.66 (s). $^{19}\text{F-NMR}$ (470 MHz, D_2O) δ : -174.8. IR (KBr) cm^{-1} : 3017, 2698, 2081, 1699, 1651, 1620, 1603. ES-MS m/z : 202 ($\text{M}^+ - 1$). $[\alpha]_D^{30} + 53.1^\circ$ ($c=0.91$, H_2O). Anal. Calcd for $\text{C}_8\text{H}_9\text{FNO}_4$: C, 47.29; H, 4.96; N, 6.89; F, 9.35. Found C, 47.29; H, 4.84; N, 6.94; F, 9.25.

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