Synthesis, in Vitro Pharmacology, Structure−Activity Relationships, and Pharmacokinetics of 3-Alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Derivatives as Potent and Selective Group II Metabotropic Glutamate Receptor Antagonists

Atsuro Nakazato,*,† Kazunari Sakagami,† Akito Yasuhara,† Hiroshi Ohta,† Ryoko Yoshikawa,‡ Manabu Itoh,§ Masato Nakamura,§ and Shigeyuki Chaki‡

Medicinal Chemistry Laboratory, Medicinal Pharmacology Laboratory, and Drug Metabolism Laboratory, Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., 1-403 Yoshino-cho, Kita-ku, Saitama-shi, Saitama 331-9530, Japan

Received February 9, 2004

Novel group II metabotropic glutamate receptor (mGluR) antagonists, 3-alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives **11** and **12**, were discovered by the incorporation of a hydroxy or alkoxyl group onto the C-3 portion of selective and potent group II mGluR agonist **5**, (1*R*,2*S*,5*R*,6*R*)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid. Among these compounds, (1*R*,2*R*,3*R*,5*R*,6*R*)-2-amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo-[3.1.0]hexane-2,6-dicarboxylic acid (−)-**11be** (MGS0039) was a highly selective and potent group II mGluR antagonist with the best pharmacokinetic profile. Compound (−)-**11be** exhibited high affinities for mGlu 2 (K_i = 2.38 ± 0.40 nM) and mGlu 3 (4.46 ± 0.31 nM) but low affinity for mGluR 7 (K_i = 664 ± 106 nM), and potent antagonist activities for mGlu 2 (IC_{50} = 20.0 ± 3.67nM) and mGluR 3 (IC_{50} = 24.0 ± 3.54 nM) but much less potent antagonist activities for mGlu 4 (IC_{50} = 1740 ± 1080 nM), mGlu 6 (IC_{50} = 2060 ± 1270 nM), mGlu 1 (IC_{50} = 93300 ± 14600 nM), and mGluR 5 (IC_{50} = 117000 ± 38600 nM). No significant agonist activities of (−)-**11be** were found for mGluRs 2, 3, 4, 6, 1, and 5 (EC_{50} > 100000 nM). Furthermore, (−)-**11be** exhibited dose-dependent oral absorption (plasma C_{max}: 214 ± 56.7, 932 ± 235, and 2960 ± 1150 ng/mL for 3 mg/kg, 10 mg/kg, and 30 mg/kg, po, respectively) and acceptable blood−brain barrier penetration (brain C_{max}: 13.2 ng/mL for 10 mg/kg, po 6 h). In this paper, we report the synthesis, in vitro pharmacological profile, and structure−activity relationships (SARs) of 3-alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives **11** and **12**, and pharmacokinetic profiles of several typical compounds.

Introduction

L-Glutamate (**1**) is a neurotransmitter at the vast majority of excitatory synapses in the brain. Normal functioning of glutamatergic synapses is required for all major functions of the brain.[1,2] The glutamate receptors are broadly classified into two types: the ionotropic glutamate receptors (iGluRs), which have an ion channel structure, and the metabotropic glutamate receptors (mGluRs), which are coupled to G-proteins. mGluRs are classified into eight subtypes, identified as subtypes 1 through 8, which are classified into three groups (I−III) on the basis of sequence homology, signal transduction mechanisms, and pharmacology.[3−9]

Group I mGluRs (mGluR 1 and mGluR 5) are positively coupled to phospholipase C, and their activation produces phosphoinositide turnover and diacylglycerol within target neurons. In contrast, both group II (mGluR 2 and 3) and group III mGluRs (mGluR 4 and mGluRs 6−8) are located in glutamatergic terminals and negatively coupled to the activity of adenyl cyclase.[9−11] mGluRs have been implicated in the pathology of major psychiatric disorders such as depression, anxiety, and schizophrenia[12] because of their critical role as modulators of synaptic transmission, ion channel activity, and synaptic plasticity.[7] Indeed, the efficacy of group II mGluR agonists in animal models and in clinical trials suggests that, by inhibiting the glutamatergic system, agonists of group II mGluRs would be useful in the treatment of many diseases and conditions such as schizophrenia,[13−15] anxiety,[16−19] and panic disorder.[20]

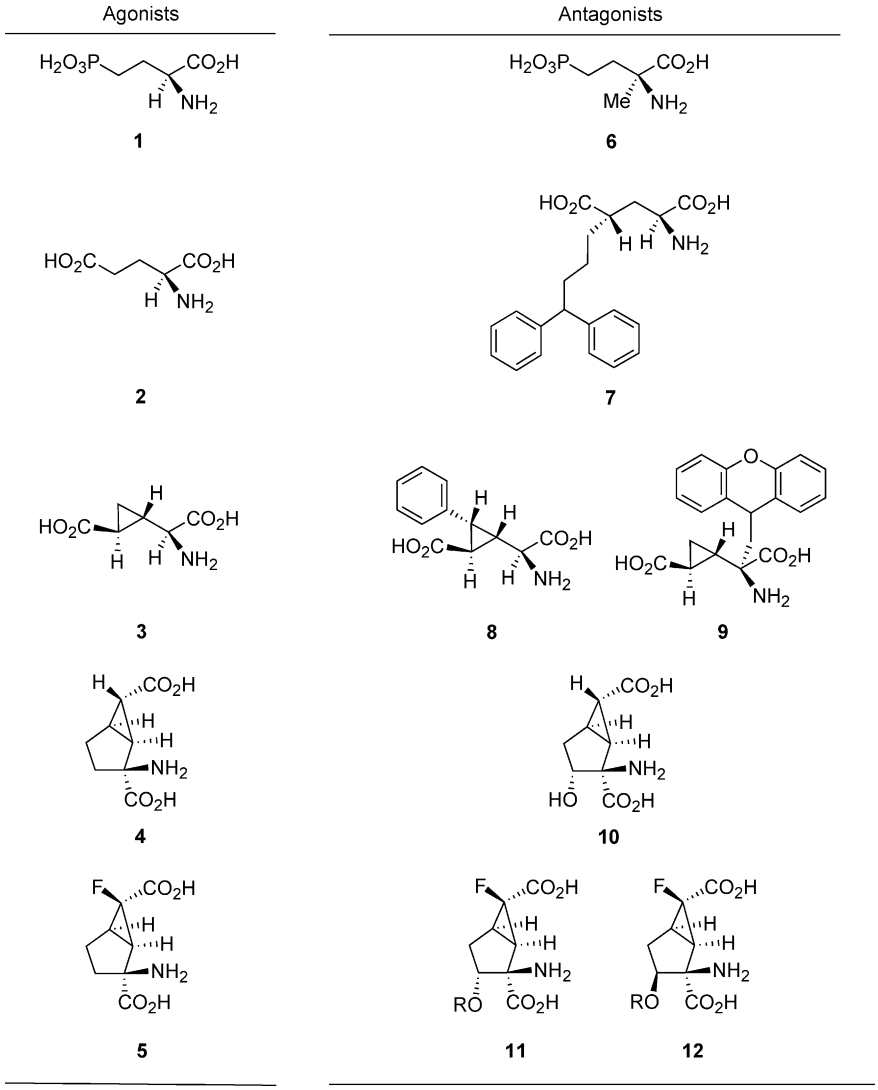
In contrast, the efficacy of antagonists for mGluRs has not been clarified in animal models and clinical trials. This might be due to the lack of potent and selective antagonists of mGluRs. We recently showed that (1*R*,2*R*,3*R*,5*R*,6*R*)-2-amino-3-(3,4-dichlorobenzyl)oxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-**11be** (R = 3,4-Cl_2PhCH_2) (0.3−3 mg/kg, ip) and (2*S*)-amino-2-((1*S*,2*S*)-2-carboxycycloprop-1-yl)-3-(9-xanthyl)propionic acid **9** (LY341495)[21,22] (0.1−3 mg/kg, ip), group II mGluR antagonists, had dose-dependent antidepressant-like effects in the rat forced swim test and mouse tail suspension test. Compound (−)-**11be** (0.3−3 mg/kg, ip) had no apparent effect in classical models of anxiety such as the rat social interaction test and rat elevated plus-maze. These findings indicate that group II mGluR antagonists, like (−)-**11be**, have antidepressant-like potential in experimental animal models.[23]

Typical mGluR antagonists that have been derived from corresponding agonists are shown in Chart 1. The

* Author to whom correspondence should be addressed. Tel: +81-48-669-3066. Fax: +81-48-652-7254. E-mail: atsu.nakazato@po.rd.taisho.co.jp.
† Medicinal Chemistry Laboratory.
‡ Medicinal Pharmacology Laboratory.
§ Drug Metabolism Laboratory.

10.1021/jm0400294 CCC: $27.50 © 2004 American Chemical Society
Published on Web 08/04/2004

Chart 1. Group II mGluR Agonists and Antagonists



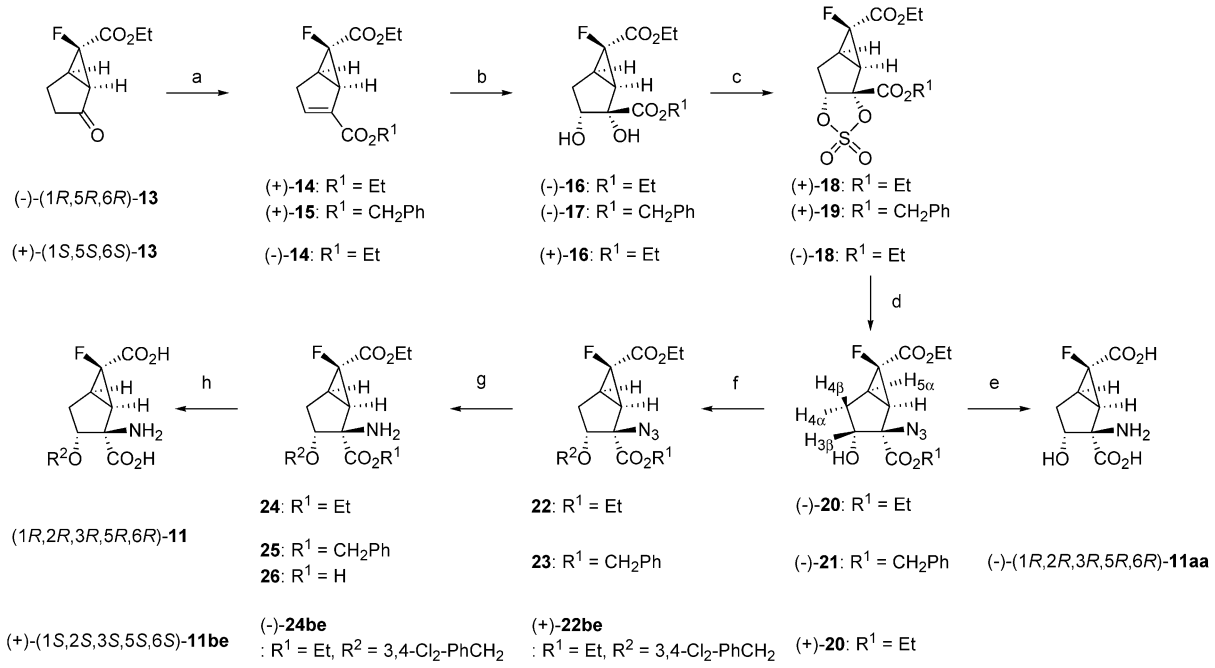
2-methyl compound of **1** (**6**, MAP-4) was found to be a weak but selective antagonist for group III mGluRs.[24] A potent and relatively selective antagonist for group II mGluRs, **7**, was obtained by introduction of a diphenylbutyl group to C-4 of glutamic acid **2**. Furthermore, introduction of a phenyl group to C-2′ of **3** or a 9-xanthylmethyl group to C-2 of **3** yielded moderately potent and very potent antagonists **8**[25] and **9**[21,22] for group II mGluRs, respectively. Compound **9** binds with very high affinity to rat brain mGluRs, with an IC_{50} of 2.9 ± 0.6 nM, and is a very potent functional antagonist, with IC_{50}s of 23 ± 4 nM and 10 ± 8 nM for human mGluRs 2 and 3, respectively. Additionally, intraperitoneal administration of **9** resulted in good plasma and acceptable brain concentrations, but the oral bioavailability of **9** was low (<5%).[22] Compound **10** is a group II mGluR antagonist, in which a hydroxyl group was introduced to C-3 of a typical group II mGluR agonist **4**.[26] Our interest was focused on differences in structures (H and OH on the C-3 position) and activities (agonist and antagonist) between **4** and **10**. On the other hand, compound **5**, a compound with a fluorine atom incorporated on the C-3 position of **4**, strongly inhibited cAMP formation with the same EC_{50} value as compound **4** and exhibited better oral activity than its original compound **4**.[13]

Thus, with the expectation that **11** and **12** would be orally active and selective antagonists of group II mGluRs, we introduced a hydroxyl group to **5** as our first goal to verify if a parallelism exists between **10** and compounds (−)-**11aa** and (−)-**12a**, by taking into consideration the analogy between the pharmacological profile of compounds **4** and **5**. 3*R* compound (−)-**11aa** (R = H) showed good binding affinities and antagonist activities for group II mGluRs as expected, but 3*S* compound (−)-**12a** exhibited obviously lower binding affinity than (−)-**11aa**.

Taking (−)-**11aa** as a lead compound, the second part of our work was devoted to the modulation of its pharmacological activity and pharmacokinetic profile through the preparation of a series of *O*-alkyl derivatives of the hydroxyl group on C-3. Among the compounds obtained, (−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-**11be** is a selective and potent group II mGluR antagonist with the best pharmacokinetic profile.

In this paper, we report the synthesis, in vitro pharmacological profile, and structure−activity relationships (SARs) of 3-alkoxy-2-amino-6-fluorobicyclo-[3.1.0]hexane-2,6-dicarboxylic acid derivatives **11** and **12**, and pharmacokinetic profiles of several typical compounds.

Scheme 1. Synthesis of (1*R*,2*R*,3*R*,5*R*,6*R*)-3-Alkoxy-, (1*S*,2*S*,3*S*,5*S*,6*S*)-3-Alkoxy-, and (1*R*,2*R*,3*R*,5*R*,6*R*)-3-Hydroxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acids **11**[a]



[a] Reagents and conditions: (a) (i) HMDS, *n*-BuLi, TfNPh, THF, −63 °C to rt; (ii) CO, $Pd(OAc)_2$, $(i\text{-}Pr)_2NEt$, PPh_3, EtOH or $PhCH_2OH$, DMF, rt. (b) 4% OsO_4, 50% NMO, MeCN, rt. (c) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 4 °C; (ii) $NaIO_4$, $RuCl_3$, H_2O, CCl_4, MeCN, rt. (d) (i) NaN_3, DMF−H_2O, 50 °C; (ii) 20% H_2SO_4, rt. (e) (i) 10% Pd/C, H_2, AcOH, H_2O, rt; (ii) 10% HCl, reflux. (f) $R^2OC(=NH)CCl_3$, TfOH, $CHCl_3$, cyclohexane, rt (typical procedure 1) or R^2OTf, 2,6-*tert*-butylpyridine, rt. (g) Me_3P, THF, H_2O, rt (typical procedure 2) or 10% Pd/C, H_2, AcOH, H_2O. (h) LiOH−H_2O, THF, H_2O, rt (typical procedure 3) or 10% HCl, reflux.

Chemistry

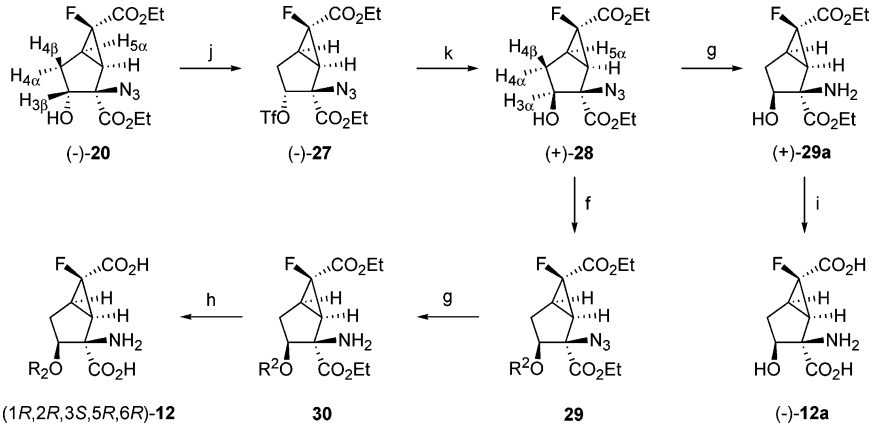
Synthesis of (1*R*,2*R*,3*R*,5*R*,6*R*)-3-alkoxy-, (1*S*,2*S*,3*S*,-5*S*,6*S*)-3-alkoxy-, and (1*R*,2*R*,3*R*,5*R*,6*R*)-3-hydroxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acids **11** is shown in Scheme 1. (1*R*,2*R*,3*R*,5*R*,6*R*)-Compounds **11aa**−**11cc** were synthesized from ethyl (−)-(1*R*,5*R*,6*R*)-6-fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylate (−)-**13**, and (+)-**11be**, the enantiomer of (−)-**11be**, was obtained from ethyl (+)-(1*S*,5*S*,6*S*)-6-fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylate (+)-**13**.

α,*β*-Unsaturated carbonyl compounds (+)- and (−)-**14** (**a**, 2,6-diethyl ester; **b**, 2-benzyl-6-ethyl ester) were obtained from optically pure compounds (−)- and (+)-**13**,[13] ethyl (−)-(1*R*,5*R*,6*R*)- and (+)-(1*S*,5*S*,6*S*)-6-fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylate, respectively, by a palladium-catalyzed reaction with carbon monoxide and an enol triflate of (−)- and (+)-**13**, which was prepared by treatment of (−)- and (+)-**13** with *N*-phenylbis(trifluoromethanesulfonimide) and lithium bis-(trimethylsilyl)amide, in the presence of the corresponding alcohol (R^1OH). Using the method of synthesis of the *β*-hydroxy α-amino acid from α,*β*-unsaturated carbonyl compound reported by Shao,[27] key intermediates (−)- and (+)-**20** and (−)-**21** were synthesized from (+)- and (−)-**14** and (+)-**15**, respectively. The oxidation reaction of the double bond in (+)- and (−)-**14** with OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) gave (−)- and (+)-**15** in good yield. In the reaction, the oxidant, OsO_4, reacted with the double bond at the opposite face of the fused cyclopropane ring to yield the single product shown in Scheme 1. Then (−)- and (+)-**16** and (−)-**17** were converted to 2,3-cyclic sulfites with $SOCl_2$ and oxidized to cyclic sulfates (+)- and (−)-**18** and (+)-**19**, respectively. Nucleophilic displacement by NaN_3 at the α-carbon of sulfates (+)- and (−)-**18** and (+)-**19** (because the cyclic sulfate acts as an excellent leaving group with good regioselectivity[28,29]) and hydrolysis provided the key intermediates (−)- and (+)-**20** and (−)-**21**. The stereochemistry of (−)- and (+)-**20** was determined from nuclear Overhauser effect spectroscopy (NOESY) spectrum. The $H_{4\alpha}$ (δ 2.50) proton and $H_{4\beta}$ (δ 2.40) proton of **20** exhibited NOESY correlations with the $H_{5\alpha}$ (δ 2.25) proton and $H_{3\beta}$ (δ 4.21−4.48), respectively.

A title compound (−)-**11aa** was obtained from the key intermediate (−)-**21** by reduction of the azido group to an amino group with reductive deprotection of 2-benzyl ester using 10% palladium/carbon catalyst and sequential hydrolysis of the ester with 10% HCl at refluxing temperature.

Etherification of the 3-hydroxy group in key intermediates (−)- and (+)-**20** and (−)-**21** was carried out by acid-catalyzed benzylation and allylation using benzyl and allyl trichloroacetimidates[30,31] or nucleopilic reaction of the 3-hydroxy group with an alkyl triflate under basic conditions. The *O*-benzylation and *O*-allylation of **17** using a trichloroacetimidate, which was prepared from 1,1,1-trichloroacetonitrile and the corresponding alcohol R^2OH, proceeded in the presence of a catalytic amount of trifluoromethanesulfonic acid to yield the corresponding benzyloxy and allyloxy compounds **18**, respectively (typical procedure 1). This acidic condition yielded frequently a mixture of 3-benzyloxy and 3-arylmethyl (R^2) compounds. The benzyl group of the 3-benzyloxy compound might be attributable to intramolecular or intermolecular transfer of the benzyl group of (−)-**21** ($R^1 = PhCH_2$). In contrast, in compound (−)-**20**,

Scheme 2. Synthesis of (1*R*,2*R*,3*S*,5*R*,6*R*)-3-Alkoxy- and (1*R*,2*R*,3*S*,5*R*,6*R*)-3-Hydroxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acids **12**[a]



[a] Reagents and conditions: (f) $R^2OC(=NH)CCl_3$, TfOH, $CHCl_3$, cyclohexane, rt (typical procedure 1) or R^2OTf, 2,6-*tert*-butylpyridine, rt. (g) Me_3P, THF, H_2O, rt (typical procedure 2) or 10% Pd/C, H_2, AcOH, H_2O. (h) LiOH−H_2O, THF, H_2O rt (typical procedure 3) or 10% HCl, reflux. (i) LiOH−H_2O, THF, H_2O, rt. (j) Tf_2O, pyridine, CH_2Cl_2, −75 °C. (k) KNO_2, 18-crown-6, DMF, rt.

the intramolecular or intermolecular transfer of the ethyl group (R^1 = Et) was not confirmed. When R^2 was 3,4-Cl_2-Ph-(Me)CH, 3,4-Cl_2-Ph-(Et)CH, 3,4-Cl_2-Ph-(Pr)-CH, and 2-Nap(Me)CH, the diastereomer mixture of **22bo** and **22bp**, **22bq** and **22br**, **22bs** and **22bt**, and **22ca** and **22cb** obtained by typical procedure 1 was separated by silica gel chromatography, respectively.

The alkylation of **17** with methyl and 3-phenylpropyl triflates under basic conditions yielded methoxy and 3-phenylpropoxy compounds **18**, respectively. Compound **19** was obtained from **18** by reduction using the Staudinger reaction[32,33] or catalytic hydrogenation with palladium/carbon catalyst. The reduction of **23ab** (**(**R^2 = Me), **23ac** (R^2 = prop-2-enyl), **22ae′** (R^2 = 1-methyl-but-2-enyl), and **22af′** (R^2 = cyclopent-2-enyl) with palladium/carbon catalyst occurred with hydrogenation of the double bond in **22ae**, **22af**, and **23ac**, and reductive deprotection of the benzyl ester of **23ab**, **23ac** to yield **26ab** (R^2 = Me), **26ad** (R^2 = 1-propyl), and **24ae** (**(**R^2 = 1-methylbutyl), **24af** (R^2 = cyclopentyl), respectively. Compound **24ax** (R^2 = 3-NH_2-$PhCH_2$) was obtained by reduction of the nitro group in **24aw** (R^2 = 3-NO_2-$PhCH_2$) with zinc powder in acetic acid. The 3-benzyloxy-substituted compounds **22** and **23** required selective reduction by the Staudinger reaction to avoid reductive cleavage of the benzyl ether at the C-3 position in compounds **22** and **23** (typical procedure 2). Finally, the optically active compounds **11ab**, **11ac**, and **11af**−**11cc** and diastereomer mixture **11ae** were obtained by ester hydrolysis in the corresponding precursors **24**, **25**, and **26** with LiOH (typical procedure 3) or HCl. Compound (−)-**11ad** was obtained by hydrogenation of the ally group in (−)-**11ac** with palladium/carbon catalyst.

Synthesis of (1*R*,2*R*,3*S*,5*R*,6*R*)-3-alkoxy- and (1*R*,2*R*,-3*S*,5*R*,6*R*)-3-hydroxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acids **12**, an epimer compound of **11**, is shown in Scheme 2.

For obtaining a key intermediate (+)-**28**, a compound in which configuration of the hydroxy group at the C-3 position in (−)-**20** was inverted, compound (−)-**20** was treated with trifluoromethanesulfonyl anhydride and pyridine to obtain (−)-**27**, and then with KNO_2 in the presence of 18-crown-6 followed by post-treatment of the resulting nitrous ester with water.[34,35] The stereochemistry of (+)-**28** was determined by NOESY. The $H_{4\alpha}$ (δ 2.85−2.92) proton of **28** exhibited NOESY correlations with the $H_{3\alpha}$ (δ 4.52−4.57) and $H_{5\alpha}$ (δ 2.21−2.25) protons, and NOESY correlation of the $H_{4\beta}$ (δ 2.15) proton to the $H_{3\alpha}$ and $H_{5\alpha}$ protons was not observed.

Compound (−)-**12a** was obtained from the key intermediate (+)-**28** by reduction utilizing the Staudinger reaction and ester hydrolysis with LiOH.

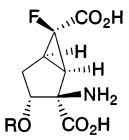
A title compound (−)-**12b** was synthesized from the key intermediate (+)-**28** by etherification with methyl triflate, reduction using the Staudinger reaction, and hydrolysis with LiOH. In the synthesis of (−)-**12b**, the manner of each reaction was similar to the corresponding reaction used for synthesis of epimer compounds **11**. Title compounds (−)-**12c** and (−)-**12d** were also obtained from (+)-**28** in a fashion similar to the synthesis of (−)-**11be** from (−)-**20** (typical procedures 1, 2, and 3).

Results and Discussion

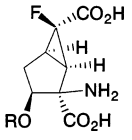
Pharmacological Profile Studies. Affinities of optically active compounds **11aa**−**11cc** (**11ae**: diastereomer mixture due to C-2 carbon of 2-pentyl group), (−)-**12a**−(−)-**12d**, and **9** for mGluR 2 were evaluated by [^{3}H]-(1*S*,2*S*,3*S*,5*R*,6*S*)-2-amino-3-fluorobicyclo[3.1.0]-hexane-2,6-dicarboxylic acid (**(**[^{3}H]-MGS0008) binding using CHO cells stably expressing mGluR 2.[13] mGluR 3 affinities of compounds (−)-**11aa**, (−)-**11ab**, (−)-**11ag**, (−)-**11al**, (−)-**11ay**, (−)-**11be**, (−)-**11bu**, and (+)-**11bz**, which were selected by mGluR 2 affinity and structural characteristics, and **9** were evaluated by [^{3}H]-(1*S*,2*S*,3*S*,5*R*,6*S*)-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid binding using CHO cells stably expressing mGluR 3.[13] Furthermore, affinities of compound (−)-**11be**, which exhibited the best pharmacokinetic profile, and **9** for mGluR 7 were evaluated by radioligand [^{3}H]-**9** binding using CHO cells stably expressing mGluR 7.[36] The K_i values obtained for mGluRs 2, 3, and 7 are shown in Table 1.

Agonist activities of selected compounds (−)-**11aa**, (−)-**11ab**, (−)-**11ag**, (−)-**11al**, (−)-**11ay**, (−)-**11be**, (−)-**11bu**, (+)-**11bz**, and **9** were evaluated by measuring agonist-dependent inhibition of forskolin-induced cyclic AMP (cAMP) formation in mGluR 2, 3, 4, 6, and 7 expressing cells,[13,37] by measuring D-*myo* Ins (1,4,5) P_3

Table 1. Binding Affinity for mGluRs 2, 3, and 7



(1*R*,2*R*,3*R*,5*R*,6*R*)-**11**



(1*R*,2*R*,3*S*,5*R*,6*R*)-**12**

		affinity[a] K_i (nM)		
compd	R	mGlu 2	mGlu 3	mGlu 7
(−)-**11aa**	H	32.9	67.1	
(−)-**11ab**	Me	39.2	88.1	
(−)-**11ac**	CH_2=CH−CH_2	7.07		
(−)-**11ad**	*n*-Pr	5.17		
11ae[b]	*n*-Pr(Me)CH	6.68		
(−)-**11af**	c-Pen	8.57		
(−)-**11ag**	$PhCH_2$	7.14	15.9	
(−)-**11ah**	$Ph(CH_2)_3$	9.83		
(−)-**11ai**	4-F-$PhCH_2$	5.55		
(−)-**11aj**	2-Cl-$PhCH_2$	4.99		
(−)-**11ak**	3-Cl-$PhCH_2$	3.28		
(−)-**11al**	4-Cl-$PhCH_2$	3.17	4.77	
(−)-**11am**	3-Br-$PhCH_2$	4.71		
(−)-**11an**	3-Me-$PhCH_2$	4.53		
(−)-**11ao**	3-CF_3-$PhCH_2$	5.72		
(−)-**11ap**	3-NC-$PhCH_2$	2.94		
(−)-**11aq**	3-HO_2C-$PhCH_2$	1.06		
(−)-**11ar**	2-Ph-$PhCH_2$	4.07		
(−)-**11as**	3-Ph-$PhCH_2$	9.34		
(+)-**11at**	4-Ph-$PhCH_2$	25.6		
(−)-**11au**	3-MeO-$PhCH_2$	5.92		
(−)-**11av**	3-PhO-$PhCH_2$	7.15		
(−)-**11aw**	3-NO_2-$PhCH_2$	7.87		
(−)-**11ax**	3-NH_2-$PhCH_2$	15.4		
(−)-**11ay**	3,4-F_2-$PhCH_2$	2.27	3.00	
(−)-**11az**	3,5-F_2-$PhCH_2$	12.4		
(−)-**11ba**	2,3-F_2-$PhCH_2$	4.25		
(−)-**11bb**	2,4-F_2-$PhCH_2$	4.71		
(−)-**11bc**	2,5-F_2-$PhCH_2$	14.4		
(−)-**11bd**	2,6-F_2-$PhCH_2$	7.02		
(−)-**11be**	3,4-Cl_2-$PhCH_2$	2.38	4.46	664
(+)-**11be**[c]	3,4-Cl_2-$PhCH_2$	>10000		
(−)-**11bf**	3,5-Cl_2-$PhCH_2$	5.61		
(−)-**11bg**	2,3-Cl_2-$PhCH_2$	4.35		
(−)-**11bh**	2,4-Cl_2-$PhCH_2$	3.89		
(−)-**11bi**	2,5-Cl_2-$PhCH_2$	11.8		
(−)-**11bj**	2,6-Cl_2-$PhCH_2$	4.30		
(−)-**11bk**	4-Cl-3-F-$PhCH_2$	4.02		
(−)-**11bl**	4-F-3-Cl-$PhCH_2$	3.57		
(−)-**11bm**	3,4,5-Cl_3-$PhCH_2$	3.67		
(−)-**11bn**	2,3,4,5,6-F_5-$PhCH_2$	3.77		
(+)-**11bo**	(*R**)-3,4-Cl_2-Ph-(Me)CH	1.45		
(−)-**11bp**	(*S**)-3,4-Cl_2-Ph(Me)CH	5.81		
(+)-**11bq**	(*R**)-3,4-Cl_2-Ph(Et)CH	1.61		
(−)-**11br**	(*S**)-3,4-Cl_2-Ph(Et)CH	3.12		
(+)-**11bs**	(*R**)-3,4-Cl_2-Ph(*n*-Pr)CH	1.48		
(−)-**11bt**	(*S**)-3,4-Cl_2-Ph(*n*-Pr)CH	3.05		
(−)-**11bu**	Ph_2CH	2.58	3.93	
(−)-**11bv**	$(4\text{-Cl-Ph})_2CH$	3.75		
(−)-**11bw**	$(4\text{-F-Ph})_2CH$	3.79		
(−)-**11bx**	$(3,4\text{-}Cl_2\text{-Ph})_2CH$	2.61		
(−)-**11by**	1-NapCH_2	5.36		
(+)-**11bz**	2-NapCH_2	2.53	5.43	
(+)-**11ca**	(*R**)-2-Nap(Me)CH	2.01		
(−)-**11cb**	(*S**)-2-Nap(Me)CH	1.79		
(−)-**11cc**	2-thiophenylCH_2	8.79		
(−)-**12a**	H	105		
(−)-**12b**	Me	190		
(−)-**12c**	3,4-Cl_2-$PhCH_2$	17.1		
(−)-**12d**	$(4\text{-Cl-Ph})_2CH$	20.2		
9		3.13	3.04	110

[a] Affinities for mGlu 2 and 3 receptors and affinities for mGlu 7 receptors were determined by binding study utilizing [^{3}H]-(1*S*,2*S*,3*S*,5*R*,6*S*)-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid and [^{3}H]-**9**, respectively. K_i values represent the means of 1−5 separate experiments obtained from 5−10 concentrations of each compound, run in duplicate. Variation between experiments was less than 30%. [b](1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-((*RS*)-1-methylbutyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid. [c](1*S*,2*S*,3*S*,5*S*,6*S*)-2-Amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid. Enantiomer of compound (−)-**11be**.

formation in mGluR 1a expressing cells[13,38,39] and by determining intracellular concentration of Ca^{2+} in mGluR 5 expressing cells.[13,40,41] Antagonist activities of these compounds were measured with 3 μM (for mGluR 3), 30 μM (for mGluRs 1, 2, 4, and 5), or 40 μM (for mGluR 6) glutamic acid.[13] The agonist and antagonist activities of the compounds are shown in Table 2.

Compound (−)-**11aa**, a compound with a hydroxyl group incorporated on the C-3 position of **5**, exhibited almost the same binding affinities for mGluR 2 (K_i = 32.9 ± 4.1 nM) and 3 (K_i = 67.1 ± 16 nM) as **5** (K_i = 22.5 ± 7.3 nM and 41.7 ± 7.1 nM for mGluRs 2 and 3, respectively[13]). Interestingly, however, (−)-**11aa** demonstrated moderate antagonist activity (IC_{50} = 476 ± 134 nM) but no significant agonist activity (EC_{50} > 100000 nM) for mGluR 2, unlike **5**, a mGluR 2 agonist with EC_{50} values of 16.6 ± 5.6 nM for mGluR 2.[13] Compared with the affinity of (−)-**11aa** for mGluRs 2 and 3, *O*-methylation of the hydroxyl group on the C-3 position of (−)-**11aa** did not affect affinity for mGlu 2 (K_i = 39.2 ± 4.1 nM) and mGlu 3 (K_i = 88.1 nM) and antagonist activity for mGluR 2 (IC_{50} = 229 ± 77.3 nM), but introduction of a larger substituent, such as propen-3-yl ((−)-**11ac**), *n*-propyl ((−)-**11ad**), (*RS*)-2-pentyl (**11ae**), cyclopentyl ((−)-**11af**), benzyl ((−)-**11ag**) or 3-phenylpropyl ((−)-**11ah**) group, yielded 3−6-fold higher binding affinities for mGluR 2 than those of methyl compound (−)-**11ab**. Among these compounds, the antagonist activity of benzyl compound (−)-**11ag** was evaluated, and (−)-**11ag** was found to exhibit a moderate antagonist activity with an IC_{50} value of 131 ± 44.9 nM for mGluR 2. These findings suggest that the agonist/antagonist activity of 2-amino-6-fluorobicyclo[3.1.0]-hexane-2,6-dicarboxylic acid derivatives on group II mGluRs is size-independently controlled by the C-3 substituent and that the potency of affinity and antagonist for group II mGluRs is dependent on the size of the substituent on the C-3 position of the derivative.

As the next step of our chemical modification, the substituent on the benzene ring of (−)-**11ag** was investigated. Introduction of a fluorine atom ((−)-**11ai**), chlorine atom ((−)-**11aj**−(−)-**11al**), bromine atom ((−)-**11am**), methyl group ((−)-**11an**), trifluoromethyl group ((−)-**11ao**), cyano group ((−)-**11ap**), carboxyl group ((−)-**11aq**), or methoxy group ((−)-**11au**) generally increased the mGluR 2 affinity of the original compound (−)-**11ag**. Chloro compounds (−)-**11ak** and (−)-**11al**, cyano compound (−)-**11ap**, and carboxyl compound (−)-**11aq** exhibited especially high affinity for mGluR 2 with K_i values of 3.28 nM, 3.17 ± 0.24 nM, 2.94 nM, and 1.06 nM, respectively. In contrast, introduction of phenyl ((−)-**11as**, (+)-**11at**), phenoxy ((−)-**11av**), nitro ((−)-**11aw**), or amino ((−)-**11ax**) groups, but not of a 2-phenyl group ((−)-**11ar**), maintained or decreased mGluR 2 affinity of the original compound (−)-**11ag**. The mGluR 2 affinities of 4-phenyl compound (+)-**11at** and amino compound (−)-**11ax** were markedly decreased, with K_i values of 25.6 nM and 15.4 nM, respectively. In case of the introduction of a phenyl group, interestingly, the substituted position strongly influenced mGluR 2 affinity. The mGluR 2 affinity of 2-substituted compound (−)-**11ar** was 2-fold and 6-fold higher than those of 3-substituted ((−)-**11as**) and 4-substituted ((+)-**11at**) compounds, respectively. These findings suggest that

Table 2. Antagonist and Agonist Activities[a]

	antagonist activity IC_{50} ± SEM (nM)						agonist activity EC_{50} (nM)					
compd	mGlu2	mGlu3	mGlu4	mGlu6	mGlu1	mGlu5	mGlu2	mGlu3	mGlu4	mGlu6	mGlu1	mGlu5
(−)-**11aa**	476 ± 134						>100000					
(−)-**11ab**	229 ± 77.3											
(−)-**11ag**	131 ± 44.9						>100000					
(−)-**11al**	29.1 ± 8.11						>100000					
(−)-**11ay**	40.8 ± 12.6											
(−)-**11be**	20.0 ± 3.67	24.0 ± 3.54	1740 ± 1080	2060 ± 1270	93300 ± 14600	11700 ± 38600	>100000	>100000	>100000	>100000	>100000	>100000
(−)-**11bu**	24.4 ± 6.53						>100000					
(+)-**11bz**	22.7 ± 7.06											
9	23.2 ± 8.75	14.2 ± 4.34	2650 ± 521	1140 ± 378	8990 ± 907	11400 ± 2700	>100000	>100000	>100000	>100000	>100000	>100000

[a] IC_{50} and EC_{50} values represent the means of 3−4 separate experiments obtained from 10 concentrations of each compound, run in duplicate.

introduction of a substituent, except for a large substituent such as a phenyl group or basic substituent such as an amino group, on the benzene ring of the benzyl group of (−)-**11ag** generally increases mGluR 2 affinity. Among these compounds, (−)-**11al** was selected for study of affinity for mGluR 3 and antagonist and agonist activities for mGluR 2 as a typical compound. Compound (−)-**11al** exhibited high affinity for mGluR 3 (K_i = 4.77 ± 1.82 nM) as well as mGluR 2 (K_i = 3.17 ± 0.24 nM) and potent antagonist activity (IC_{50} = 29.1 ± 8.11 nM) but no significant agonist activity (IC_{50} > 100000 nM) for mGluR 2.

The dihalo compounds (−)-**11ay**−(−)-**11be** and (−)-**11bf**−(−)-**11bl** generally exhibited high affinities for mGluR 2, and the order of substituted position for mGluR 2 affinity was, from high to low, 3,4 ≥ 2,3, 2,4, 2,6 ≥ 3,5, 2,4. Furthermore, tri- and pentahalo compounds (−)-**11bm** and (−)-**11bn** exhibited high affinities for mGluR 2 as well as dihalo compounds. Among these compounds, the in vitro pharmacologies of (−)-**11ay** and (−)-**11be** were investigated as those of typical compounds. Both (−)-**11ay** and (−)-**11be** exhibited high affinity for mGluR 3 (K_i = 3.00 ± 0.61 nM and 4.46 ± 0.40 nM, respectively) as well as mGluR 2 (K_i = 2.27 ± 0.271 nM and 2.38 ± 0.40 nM, respectively). Furthermore, compound (−)-**11be** exhibited lower affinity (K_i = 664 ± 106 nM) for mGluR 7 than typical antagonist **9** (K_i = 110 ± 13.7 nM). Compounds (−)-**11ay** and (−)-**11be** exhibited potent antagonist activities (EC_{50} = 40.8 ± 12.6 nM and 20.0 ± 3.67 nM, respectively) for mGluR 2, but no significant agonist activities (EC_{50} > 100000 nM and > 100000 nM, respectively) for mGluR 2. Compound (−)-**11be** exhibited potent antagonist activity for mGluR 3 (IC_{50} = 24.0 ± 3.54 nM) as well as mGluR 2, much less potent antagonist activities for mGluRs 4 (IC_{50} = 1740 ± 1080 nM), 6 (IC_{50} = 2060 ± 1270 nM), 1 (IC_{50} = 93300 ± 14600 nM), and 5 (IC_{50} = 117000 ± 38600 nM), and no significant agonist activities for mGluRs 2, 3, 4, 6, 1, and 5 (EC_{50} > 100000 nM). Compound **9** has affinity for mGluRs 7 and 8.[36] In our study, compound (−)-**11be** exhibited 300-fold lower affinity for mGluR7 than for mGluR2, while **9** exhibited 35-fold lower affinity for mGluR7 than for mGluR2, as determined by [^{3}H]-**9** binding to recombinant mGluR 7. Thus, (−)-**11be** may display greater specificity for group II mGluRs, although its effects on mGluR 8 have yet to be determined. In addition, (−)-**11be** did not interact with other receptors and transporters including *N*-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl isoxazole-4-propionate (AMPA), and kainite receptors.[23] Moreover, in a preliminary experiment, (−)-**11be** did not inhibit glutamate transport through glutamate transporters such as excitatory amino acid transporter (EAAT) 1, EAAT2, and EAAT3 even at 10 μM.[23] These findings suggest that (−)-**11be** is one of the most potent and selective antagonists for group II mGluRs obtained to date.

Next, introduction of a low alkyl group, such as methyl, ethyl, and propyl, on the methylene of the benzyl group of (−)-**11be** was studied. Optically active compounds (+)-**11bo** (Me**)**, (+)-**11bq** (Et**)**, and (+)-**11bs** (Pr**)** exhibited slightly higher affinity for mGluR 2 than the original methylene compound (−)-**11be**, and these affinities were determined to be stereoselective. Compounds (+)-**11bo** (K_i = 1.45 nM), (+)-**11bq** (K_i = 1.61 nM), and (+)-**11bs** (K_i = 1.48 nM) exhibited 2−4-fold higher mGluR 2 affinity than the corresponding isomers (−)-**11bp** (K_i = 5.81 nM), (−)-**11br** (K_i = 3.12 nM), and (−)-**11bt** (K_i = 3.05 nM). Diphenylmethyl compounds (−)-**11bu**−(−)-**11bx** exhibited high affinities for mGluR 2, which were almost the same as those of the corresponding monophenyl compounds ((−)-**11bu** vs (−)-**11ag**, (−)-**11bv** vs (−)-**11al**, (−)-**11bw** vs (−)-**11ai**, and (−)-**11bx** vs (−)-**11be**), except for (−)-**11bu**. However, the affinity of (−)-**11bx** was slightly lower than those of low alkyl compounds ((−)-**11bx** vs (+)-**11bo**, (+)-**11bq**, and (+)-**11bs**). These findings suggest that two phenyl rings are not required for high mGluR 2 affinity, and that one phenyl group plays the important role in the interaction between mGluR 2 and ligand. Among these compounds, compound (−)-**11bu** exhibited high affinity for mGluR 3 (K_i = 3.93 ± 0.88 nM), as well as mGluR 2 (K_i = 2.58 ± 0.42 nM), and high antagonist activity (IC_{50} = 24.4 ± 6.53 nM) but no significant agonist activity (ED_{50} > 100000 nM) for mGluR 2.

Naphthyl and thiophenyl compounds ((−)-**11by**, (+)-**11bz**, and (−)-**11cc**), especially 2-naphthyl compound (+)-**11bz** (K_i = 2.53 ± 0.13 nM), exhibited high affinity for mGluR 2 as well as phenyl compounds (−)-**11ag**−(−)-**11as**, (+)-**11at**, (−)-**11au**−(−)-**11be**, (−)-**11bf**−(−)-**11bn**. Furthermore, introduction of a methyl group on the methylene of the naphthylmethyl group of (+)-**11bz** slightly increased the binding affinity of original compound (+)-**11bz** for mGluR 2, and this affinity was determined to be slightly stereoselective ((+)-**11ca**, K_i = 2.01 nM; (−)-**11cb**, K_i = 1.79 nM). These increases and the stereoselectivity of mGluR 2 affinity found in naphthyl compounds (+)-**11bz**, (+)-**11ca**, and (−)-**11cb** were lower than those of dichlorophenyl compounds (−)-**11be**, (+)-**11bo**, and (−)-**11bp**. Compound (+)-**11bz** exhibited high affinity not only for mGlu 2 but also for mGluR 3 (K_i = 5.43 ± 1.10 nM), and exhibited potent antagonist activity for mGluR 2 (IC_{50} = 22.7 ± 7.06 nM).

Last, structure−activity relationships concerning stereochemistry on the bicyclo[3.1.0]hexane ring were investigated. The enantiomer of (−)-**11be**, compound (+)-**11be**, exhibited no significant affinity for mGluR 2 (K_i > 10000 nM). Furthermore, *S* isomers at the C-3 position on the bicyclo[3.1.0]hexane ring, (−)-**12a**, (−)-**12b**, (−)-**12c**, and (−)-**12d**, exhibited 3−7-fold lower affinity for mGluR 2 than the corresponding *R* isomers (−)-**11aa**, (−)-**11ab**, (−)-**11be**, and (−)-**11bv**. These stereoselective affinities for mGluR 2 suggest that affinity depends largely on stereochemistry on the bicyclo[3.1.0]hexane ring, that the 1*R*,2*R*,5*R*,6*R* conformation is essential for mGluR 2 affinity, and that the 3*R* conformation is ideal for exhibition of high mGluR 2 affinity.

Pharmacokinetic Profile Study. Pharmacokinetic parameters of compounds (−)-**11al**, (−)-**11ay**, (−)-**11be**, (−)-**11bu**, and (+)-**11bz** after oral administration to rats at doses of 3, 10 and 30 mg/kg are shown in Table 3. Brain and plasma levels and pharmacokinetic parameters of compounds (−)-**11al**, (−)-**11ay**, (−)-**11be**, (−)-**11bu**, and (+)-**11bz** after oral administration to rats at a dose of 10 mg/kg are shown in Table 4. The sample analyses were performed on an LC/ESI-MS/MS system utilizing (−)-**11ay** (for measurement of (−)-**11be**) and

Table 3. Pharmacokinetic Parameters of Compounds (−)-**11al**, (−)-**11ay**, (−)-11**be**, (−)-**11bu**, and (+)-**11bz** after Oral Administration to Rats at Doses of 3, 10, and 30 mg/kg[a]

compd	dos (mg/kg)	T_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ Lambda z (h)	AUCinf (predicted) (h ng/mL)
(−)-**11al**	3	1.3 ± 0.6	76.6 ± 5.0	1.67 ± 0.25	383 ± 35.5
	10	2.3 ± 1.5	272 ± 18.1	3.75 ± 0.50	1770 ± 388
	30	2.7 ± 1.2	651 ± 65.9	3.28 ± 1.33	6130 ± 1050
(−)-**11ay**	3	1.3 ± 0.6	82.3 ± 30.5	3.47 ± 2.16	474 ± 170
	10	1.7 ± 0.6	297 ± 117	1.78 ± 1.03	1370 ± 404
	30	1.2 ± 0.8	635 ± 94.8	3.62 ± 0.41	3340 ± 38.8
(−)-**11be**	3	2.0 ± 0.0	214 ± 56.7	2.15 ± 0.63	1240 ± 67.4
	10	2.7 ± 1.2	932 ± 235	2.76 ± 0.06	6260 ± 2320
	30	3.3 ± 1.2	2960 ± 1150	2.77 ± 0.13	19300 ± 2020
(−)-**11bu**	3	0.7 ± 0.3	25.0 ± 12.0	1.62 ± 0.07	105 ± 48.6
	10	1.8 ± 1.9	85.1 ± 20.7	2.20 ± 1.27	479 ± 126
	30	1.0 ± 0.9	312 ± 15.7	3.63 ± 0.88	1600 ± 54.6
(+)-**11bz**	3	4.0 ± 0.0	65.9 ± 27.0	3.66 ± 0.42	635 ± 201
	10	2.7 ± 1.2	374 ± 136	2.74 ± 0.20	2820 ± 1300
	30	2.7 ± 1.2	965 ± 67.8	2.93 ± 0.14	7580 ± 1900

[a] Results are expressed as the mean ± SD, $n = 3$.

(−)-**11be** (for measurement of (−)-**11al**, (−)-**11ay**, (−)-**11bu**, and (+)-**11bz**) as internal standards.

Compound (−)-11al. Dose Response. After oral administration of 3 mg/kg (−)-**11al** to fasting rats, the plasma concentration reached a C_{max} of 76.6 ± 5.00 ng/mL at 1.3 ± 0.6 h, and declined with a half-life of 1.67 ± 0.25 h. The AUCinf was 383 ± 35.5 ng h/mL. At 10 mg/kg, plasma concentration reached a C_{max} of 272 ± 48.1 ng/mL at 2.3 ± 1.5 h, and declined with a half-life of 3.75 ± 0.50 h. The AUCinf was 1770 ± 388 ng h/mL. At 30 mg/kg, plasma concentration reached a C_{max} of 651 ± 65.9 ng/mL at 2.7 ± 1.2 h, and declined with a half-life of 3.28 ± 1.33 h. The AUCinf was 6130 ± 1050 ng h/mL. The ratios of C_{max} and AUCinf were 1.0:3.6:8.5 and 1.0:4.6:16.0 at doses of 3, 10, and 30 mg/kg, respectively.

Blood−Brain Barrier Penetration. The mean maximum plasma level of (−)-**11al** was reached at 3 h and was a mean of 225 ng/mL. Plasma levels were below the limit of detection (1 ng/mL) at 24 h post-dose, and the half-life estimated from the levels obtained by 6 h was 2.5 h. The AUCinf was 1330 ng h/mL. The mean maximum cerebral level of (−)-**11al** was reached at 3 h, and was a mean of 3.66 ng/g. Although the level in brain was below the limit of detection (1.5 ng/g) at 24 h post-dose, brain levels were fairly constant from 1 to 6 h after dosing. Therefore, half-life could not be estimated. The cerebrum/plasma ratios of (−)-**11al** at 1, 3, and 6 h were 0.01, 0.02, and 0.03, respectively. The rate of elimination from the cerebrum might be slower than that from plasma.

Compound (−)-11ay. Dose Response. After oral administration of 3 mg/kg (−)-**11ay** to fasting rats, the plasma concentration reached a C_{max} of 82.3 ± 30.5 ng/mL at 1.3 ± 0.6 h, and declined with a half-life of 3.47 ± 2.16 h. The AUCinf was 474 ± 170 ng h/mL. At 10 mg/kg, plasma concentration reached a C_{max} of 297 ± 117 ng/mL at 1.7 ± 0.6 h, and declined with a half-life of 1.78 ± 1.03 h. The AUCinf was 1370 ± 404 ng h/mL. At 30 mg/kg, plasma concentration reached a C_{max} of 635 ± 94.8 ng/mL at 1.2 ± 0.8 h, and declined with a half-life of 3.62 ± 0.41 h. The AUCinf was 3340 (38.8) ng h/mL. The ratios of C_{max} and AUCinf were 1.0:3.6:7.3 and 1.0:2.9:7.0 at doses of 3, 10, and 30 mg/kg, respectively.

Blood−Brain Barrier Penetration. The mean maximum plasma level of (−)-**11ay** was reached at 1 h and was a mean of 213 ng/mL. After peaking, plasma concentration decreased with an estimated half-life of 2.8 h. The AUCinf was 1210 ng h/mL. The mean maximum cerebral level of (−)-**11ay** was reached at 3 h and was a mean of 3.11 ng/g. After peaking, cerebral concentrations decreased with an estimated half-life of 19.5 h. The cerebrum/plasma ratios of (−)-**11ay** at 1, 3, 6, and 24 h were 0.01, 0.02, 0.06, and 1.07, respectively. The rate of elimination from the cerebrum was slower than that from plasma.

Compound (−)-11be. Dose Response. After oral administration of 3 mg/kg (−)-**11be** to fasting rats, the plasma concentration reached a C_{max} of 214 ± 56.7 ng/mL at 2.0 ± 0.0 h, and declined with a half-life of 2.15 ± 0.63 h. The AUCinf was 1240 ± 67.5 ng h/mL. At 10 mg/kg, plasma concentration reached a C_{max} of 932 ± 235 ng/mL at 2.7 ± 1.2 h, and declined with a half-life of 2.76 ± 0.06 h. The AUCinf was 6260 ± 2320 ng h/mL. At 30 mg/kg, plasma concentration reached a C_{max} of 2960 ± 1150 ng/mL at 3.3 ± 1.2 h, and declined with a half-life of 2.77 ± 0.13 h. The AUCinf was 19300 ± 2020 ng h/mL. The ratios of C_{max} and AUCinf were 1.0:4.4:13.9 and 1.0:5.1:15.6 at doses of 3, 10, and 30 mg/kg, respectively.

Blood−Brain Barrier Penetration. The mean maximum plasma level of (−)-**11be** was reached at 6 h and was a mean of 492.3 ng/mL. After peaking, plasma concentrations decreased with an estimated half-life of

Table 4. Brain and Plasma Levels and Pharmacokinetics Parameters of Compounds (−)-**11al**, (−)-**11ay**, (−)-**11be**, (−)-**11bu**, and (+)-**11bz** after Peroral Dosing to Rats at a Dose of 10 mg/kg

	Brain and Plasma Concentrations (ng/mL or g)[a]									
	(−)-**11al**		(−)-**11ay**		(−)-**11be**		(−)-**11bu**		(+)-**11bz**	
	plasma	brain	plasma	brain	plasma	brain	plasma	brain	plasma	brain
1 (h)	176 ± 39.3	2.51 ± 0.20	213 ± 11.4	3.06 ± 0.34	364 ± 273	3.88 ± 2.46	61.3 ± 24.0	0.00 ± 0.00	121 ± 9.0	1.42 ± 0.21
3 (h)	225 ± 39.9	3.66 ± 0.75	179 ± 50.0	3.11 ± 0.69	429 ± 28.9	8.02 ± 235	37.6 ± 2.5	0.00 ± 0.00	252 ± 32.5	3.64 ± 0.55
6 (h)	98.2 ± 7.7	3.39 ± 1.08	41.1 ± 9.8	2.40 ± 0.40	492 ± 344	13.2 ± 6.75	23.1 ± 11.5	2.04 ± 0.60	210 ± 11.1	8.72 ± 6.64
24 (h)	0.00 ± 0.00	0.00 ± 0.00	0.80 ± 0.70	1.39 ± 1.21	2.10 ± 0.20	4.22 ± 1.30	0.20 ± 0.10	0.51 ±0.89	2.20 ± 1.20	0.25 ± 0.02
	Parameters									
T_{max} (mg/kg)	3.0	3.0	1.0	3.0	6.0	6.0	1.0	6.0	3.0	6.0
C_{max} (ng/mL)	225	3.66	213	3.11	492	13.2	61.3	2.04	252	8.72
$t_{1/2}$ Lambda z (h)	2.50		2.80	19.5	2.30	10.9	2.80	9.00	2.90	7.10
AUCinf (predicted) (h ng/mL)	1330		1210	88.7	6810	269	431	32.6	3040	132

[a] Results are expressed as the mean ± SD, $n = 3$.

2.3 h. The AUCinf was 6813.0 ng h/mL. The mean maximum cerebral level of (−)-**11be** was reached at 6 h and was a mean of 13.22 ng/g. After peaking, cerebral concentrations decreased with an estimated half-life of 10.9 h. The cerebrum/plasma ratios of (−)-**11be** at 1, 3, 6, and 24 h were 0.01, 0.02, 0.03, and 1.99, respectively. The rate of elimination from the cerebrum was slower than that from plasma.

Compound (−)-11bu. Dose Response. After oral administration of 3 mg/kg (−)-**11bu** to fasting rats, the plasma concentration reached a C_{max} of 25.0 ± 12.0 ng/mL at 0.7 ± 0.3 h, and declined with a half-life of 1.62 ± 0.07 h. The AUCinf was 105 ± 48.6 ng h/mL. At 10 mg/kg, plasma concentration reached a C_{max} of 85.1 ± 20.7 ng/mL at 1.8 ± 1.9 h, and declined with a half-life of 2.20 ± 1.27 h. The AUCinf was 479 ± 126 ng h/mL. At 30 mg/kg, plasma concentration reached a C_{max} of 312 ± 15.7 ng/mL at 1.0 ± 0.9 h, and declined with a half-life of 3.63 ± 0.88 h. The AUCinf was 1600 ± 54.6 ng h/mL. The ratios of C_{max} and AUCinf were 1.0:3.4:12.3 and 1.0:4.6:15.3 at doses of 3, 10, and 30 mg/kg, respectively.

Blood−Brain Barrier Penetration. The mean maximum plasma level of (−)-**11bu** was reached at 1.0 h and was a mean of 61.3 ng/mL. After peaking, plasma concentrations decreased with an estimated half-life of 2.80 h. The AUCinf was 431 ng h/mL. The mean maximum cerebral level of (−)-**11bu** was reached at 6 h and was a mean of 2.04 ng/g. After peaking, cerebral concentrations decreased with an estimated half-life of 9 h. The cerebrum/plasma ratios of (−)-**11bu** at 1, 3, 6, and 24 h were 0.00, 0.00, 0.10, and 1.40, respectively. The rate of elimination from the cerebrum was slower than that from plasma.

Compound (+)-11bz. Dose Response. After oral administration of 3 mg/kg (+)-**11bz** to fasting rats, the plasma concentration reached a C_{max} of 65.9 ± 27.0 ng/mL at 4.0 ± 0.0 h, and declined with a half-life of 3.66 ± 0.42 h. The AUCinf was 635 ± 201 ng h/mL. At 10 mg/kg, plasma concentration reached a C_{max} of 374 ± 136 ng/mL at 2.7 ± 1.2 h, and declined with a half-life of 2.74 ± 0.20 h. The AUCinf was 2820 ± 1300 ng h/mL. At 30 mg/kg, plasma concentration reached a C_{max} of 965 ± 67.8 ng/mL at 2.7 ± 1.2 h, and declined with a half-life of 2.93 ± 0.14 h. The AUCinf was 7580 ± 1900 ng h/mL. The ratios of C_{max} and AUCinf were 1.0:5.7:14.7 and 1.0:4.4:11.9 at doses of 3, 10, and 30 mg/kg, respectively.

Blood−Brain Barrier Penetration. The mean maximum plasma level of (+)-**11bz** was reached at 3 h and was a mean of 251.7 ng/mL. After peaking, plasma concentrations decreased with an estimated half-life of 2.9 h. The AUCinf was 3042.6 ng h/mL. The mean maximum cerebral level of (+)-**11bz** was reached at 6 h and was a mean of 8.72 ng/g. After peaking, cerebral concentrations decreased with an estimated half-life of 7.1 h. The cerebrum/plasma ratios of (+)-**11bz** at 1, 3, 6, and 24 h were 0.01, 0.01, 0.04, and 0.86, respectively. The rate of elimination from the cerebrum was slower than that from plasma.

Thus, five selected 3-alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives (−)-**11al**, (−)-**11ay**, (−)-**11be**, (−)-**11bu**, and (+)-**11bz** exhibited dose-dependent increases in plasma level, and compound (−)-**11be** exhibited the highest plasma level among the five compounds. Compound (−)-**11be** exhibited the best oral absorption.

The lower rate of elimination from the cerebrum than from plasma can be considered a distinct feature of 3-alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives. Of the above five compounds, compound (−)-**11be** exhibited the best PK profile. Furthermore, compound (−)-**11be** exhibited higher plasma (492 ng/mL) and brain (13.2 ng/g) concentrations than known group II mGluR antagonist **9** (plasma, 64.1 ng/mL; brain, 7.4 ng/g)[22] at oral administration of 10 mg/kg to rats. Thus, compound (−)-**11be** may be useful for exploring the functions of group II mGluRs and in the treatment of depression,[23] not only because it is a potent and selective antagonist of group II mGluRs but also because it exhibits a good absorption and blood−brain barrier penetration.

Conclusions

In this paper, we have presented the in vitro pharmacological and pharmacokinetic profiles of novel 3-alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives **11** and its C3-isomer **12**. Incorporation of a hydroxyl or alkoxy group on the C-3 position of group II mGluR agonist **5** produced a group II mGluR antagonist despite the size of the alkoxy group. Furthermore, it was found that the affinity depended largely on the stereochemistry of the bicyclo[3.1.0]hexane ring, that the 1*R*,2*R*,5*R*,6*R* conformation is essential for mGluR 2 affinity, and that the 3*R* conformation is ideal for exhibition of high mGluR 2 affinity.

Of the compounds presented, (−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]-hexane-2,6-dicarboxylic acid (−)-**11be**, a compound with a 3,4-dichlorobenzyloxy group incorporated on the C-3 position of **5**, is the best group II mGluR antagonist obtained to date with regard to affinity, selectivity, oral absorption, and blood−brain barrier penetration. Consistent with a previous demonstration of the antidepressant-like activity of (−)-**11be**,[23] (−)-**11be** may be useful for exploring the functions of group II mGluRs and in the treatment of depression.

Experimental Section

Chemistry. Melting points were determined on a Yanaco MP-500D melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained using a Varian Gemini 2000 (200 MHz) or Varian Unity Inova 300 (300 MHz). ^{13}C NMR and ^{1}H NMR spectra were obtained using a 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. Mass spectra (MS) were obtained on a JEOL JMS-SX102 (FAB) or Micromass Platform LC (ion spray). 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*R*,5*R*,6*R*)-6-Fluorobicyclo[3.1.0]hex-2-ene-2,6-dicarboxylic Acid Diethyl Ester (+)-14. To a solution of bis(trimethylsilyl)amine (HMDS) (137 mL, 0.651 mol) in tetrahydrofuran (THF) (700 mL) was added BuLi (2.66 M hexane solution, 245 mL, 0.651 mol) under a nitrogen atmosphere at

−63 to −54 °C. After the mixture was stirred for 1 h, to the mixture was added a solution of ethyl (−)-(1*R*,5*R*,6*R*)-6-fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylate (−)-**13** (101 g, 0.542 mol) in THF (340 mL) at −63 to −52 °C, and the resultant was stirred for 1 h. A solution of *N*-phenylbis(trifluoromethansulfonimide) (213 g, 0.597 mol) in THF (700 mL) was added to the mixture at −63 to −45 °C with cooling in a dry ice−acetone bath. After removal of the dry ice−acetone bath, the resultant mixture was stirred for 2.5 h. The reaction mixture was diluted with ether. The ether solution was washed with saturated $NaHCO_3$ (×3) and saturated brine, dried with Na_2SO_4, concentrated under reduced pressure, and chromatographed (hexane/AcOEt = 30:1−5:1) to yield a colorless oil (175 g). A mixture of the obtained colorless oil (175 g), diisopropylethylamine (95.1 mL, 0.550 mol), triphenylphosphine (8.65 g, 33.0 mmol), and $Pd(OAc)_2$ (3.70 g, 16.5 mmol) in a mixture of ethanol (875 mL) and *N*,*N*-dimethylformamide (DMF) (875 mL) was stirred for 5.5 h at room temperature under a carbon monoxide atmosphere. The mixture was diluted with 1 N HCl and extracted with ether (×6). The combined ether layer was washed with saturated $NaHCO_3$ (×4) and saturated brine, dried with Na_2SO_4, evaporated, and chromatographed (hexane/AcOEt = 30:1−10:1) to yield (+)-**14** (92.6 g, 71%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.31 (3 H, t, J = 7.0 Hz), 1.33 (3 H, t, J = 7.0 Hz), 2.37−2.51 (1 H, m), 2.65−2.81 (1 H, m), 2.88−3.04 (1 H, m), 3.10 (1 H, dd, J = 7.5, 2.5 Hz), 4.12−4.40(4 H, m), 6.77−6.79 (1 H, m); MS (ion spray) (positive) m/z 265 $(M + Na)^+$; $[\alpha]^{21}_D = +158.0°$ (c = 1.5, $CHCl_3$).

(−)-(1*S*,5*S*,6*S*)-6-Fluorobicyclo[3.1.0]hex-2-ene-2,6-dicarboxylic Acid Diethyl Ester (−)-14. In a manner similar to the preparation of (+)-**14** from (−)-**13** and ethanol, (−)-**14** (4.33 g, 66%) was obtained from (+)-**13** (5.06 g, 27.2 mmol) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.31 (3 H, t, J = 7.0 Hz), 1.33 (3 H, t, J = 7.0 Hz), 2.37−2.51 (1 H, m), 2.65−2.81 (1 H, m), 2.88−3.04 (1 H, m), 3.10 (1 H, dd, J = 7.5, 2.5 Hz), 4.12−4.40(4 H, m), 6.77−6.79 (1 H, m); MS (ion spray) (positive) m/z 265 $(M + Na)^+$; $[\alpha]^{28}_D = -165.4°$ (c = 1.5, $CHCl_3$).

(+)−(1*R*,5*R*,6*R*)-6-Fluorobicyclo[3.1.0]hex-2-ene-2,6-dicarboxylic Acid 2-Benzyl 6-Ethyl Ester (+)-15. In a manner similar to the preparation of (+)-**14** from (−)-**13** and ethanol, (+)-**15** (6.42 g, 33%) was obtained from (−)-**13** (12.0 g, 64.5 mmol) and benzyl alcohol (12.5 g) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.33 (3 H, t, J = 7.2 Hz), 2.41−2.47 (1 H, m), 2.71−2.80 (1 H, m), 2.89−3.00 (1 H, m) 3.12 (1 H, dd, J = 7.5, 2.6 Hz), 4.28 (2 H, q, J = 7.2 Hz), 5.18 (1 H, d, J = 12.4 Hz), 5.24 (1 H, d, J = 12.4 Hz), 6.81−6.83 (1 H, m), 7.32−7.38 (5 H, m); MS (ion spray) (positive) m/z 327 $(M + Na)^+$; $[\alpha]^{29}_D = +184.0°$ (c = 0.20, $CHCl_3$).

(−)-(1*R*,2*S*,3*R*,5*R*,6*R*)-6-Fluoro-2,3-dihydroxybicyclo-[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (−)-16. A mixture of (+)-**14** (92.4 g, 0.381 mol), 50% aqueous *N*-methylmorpholine *N*-oxide (NMO) (160 mL, 0.762 mol) and 4% aqueous OsO_4 (121 mL, 19.1 mmol) in a mixture of MeCN (1.76 L) and H_2O (680 mL) was stirred for 1 h at room temperature. Na_2SO_3 was added to the reaction mixture with ice-cooling, and the resultant mixture was stirred for 1 h. The mixture was filtered using a Celite pad, and the filtrate was extracted with AcOEt (×2). The combined AcOEt layer was washed with saturated brine, dried with Na_2SO_4, evaporated, and chromatographed (hexane/AcOEt = 4:1−1:1) to yield (−)-**16** (95.6 g, 91%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.31 (6 H, t, J = 7.3 Hz), 2.03−2.34 (3 H, m), 2.40−2 0.55 (1 H, m), 2.70 (1 H, d, J = 9.2 Hz), 4.09 (1 H, s), 4.18−4.47 (5H, m); MS (ion spray) (negative) m/z 275 $(M - 1)^-$; $[\alpha]^{27}_D = -69.1°$ (c = 1.4, $CHCl_3$).

(+)−(1*S*,2*R*,3*S*,5*S*,6*S*)-6-Fluoro-2,3-dihydroxybicyclo-[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (+)-16. In a manner similar to the preparation of (−)-**16** from (+)-**14**, (+)-**16** (4.42 g, 90%) was obtained from (−)-**14** (4.30 g, 17.8 mmol) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.31 (6 H, t, J = 7.3 Hz), 2.03−2.34 (3 H, m), 2.40−2 0.55 (1 H, m), 2.70 (1 H, d, J = 9.2 Hz), 4.09 (1 H, s), 4.18−4.47 (5H, m); MS (ion spray) (negative) m/z 275 $(M - 1)^-$; $[\alpha]^{27}_D = +78.8°$ (c = 2.0, $CHCl_3$).

(−)-(1*R*,2*S*,3*R*,5*R*,6*R*)-6-Fluoro-2,3-dihydroxybicyclo-[3.1.0]hexane-2,6-dicarboxylic Acid 2-Benzyl 6-Ethyl Ester (−)-17. In a manner similar to the preparation of (−)-**16** from (+)-**14**, (−)-**17** (12.1 g, 91%) was obtained from (+)-**15** (12.0 g, 39.4 mmol) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.29 (3 H, t, J = 7.2 Hz), 2.06−2.21(2 H, m), 2.30 (1 H, dd, J = 7.6, 2.6 Hz), 2.47 (1 H, dd, J = 7.6, 13.2 Hz), 2.50 (1 H, dd, J = 1.2, 9.2 Hz), 4.02 (1 H, s), 4.24 (2 H, q, J = 7.2 Hz), 4.34−4.46 (1 H, m), 5.23 (1 H, d, J = 12.5 Hz), 5.28 (1 H, d, J = 12.5 Hz), 7.27−7.42 (5 H, m); MS (ion spray) (positive) m/z 361 $(M + Na)^+$; $[\alpha]^{29}_D = -45.8°$ (c = 0.20, $CHCl_3$).

(+)−(1*R*,1a*R*,1b*S*,4a*R*,5a*R*)-1-Fluoro-3,3-dioxotetrahydro-2,4-dioxa-3λ^6-thiacyclopropa[*a*]pentalene-1,1b-dicarboxylic Acid Diethyl Ester (+)-18. $SOCl_2$ (37.6 mL) was added to a solution of (−)-**16** (95.4 g, 0.345 mol) and Et_3N (106 mL, 0.760 mol) in CH_2Cl_2 (1.24 L) with ice-cooling, and the mixture was stirred for 0.5 h. H_2O was added to the reaction mixture, and the CH_2Cl_2 layer was separated. The CH_2Cl_2 layer was washed with H_2O and saturated brine, dried with $MgSO_4$, and evaporated. The residue was dissolved in a mixture of CCl_4 (640 mL), MeCN (640 mL), and H_2O (760 mL). $NaIO_4$ (96.0 g, 0.449 mol) and $RuCl_3 \cdot H_2O$ (655 mg) were added to the solution with ice-cooling, and the resulting mixture was stirred for 1 h. The mixture was filtered using a Celite pad, the filtrate was partitioned into organic and aqueous layers, and the aqueous layer was extracted with ether. The combined organic layer was washed with saturated brine, dried with $MgSO_4$, evaporated, and chromatographed (hexane/AcOEt = 4:1) to yield (+)-**18** (109 g, 93%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.33 (3 H, t, J = 7.0 Hz), 1.34 (3 H, t, J = 7.0 Hz), 2.52−2.94 (4 H, m), 4.23−4.47 (4 H, m), 5.40−5.53 (1 H, m); MS (ion spray) (positive) m/z 361 $(M + Na)^+$; $[\alpha]^{28}_D = +18.3°$ (c = 1.0, $CHCl_3$).

(−)-(1*S*,1a*S*,1b*R*,4a*S*,5a*S*)-1-Fluoro-3,3-dioxotetrahydro-2,4-dioxa-3λ^6-thiacyclopropa[*a*]pentalene-1,1b-dicarboxylic Acid Diethyl Ester (−)-18. In a manner similar to the preparation of (+)-**18** from (−)-**16**, (−)-**18** (4.90 g, 92 %) was obtained from (+)-**16** (4.36 g, 15.8 mmol) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.33 (3 H, t, J = 7.0 Hz), 1.34 (3 H, t, J = 7.0 Hz), 2.52−2.94 (4 H, m), 4.23−4.47 (4 H, m), 5.40−5.53 (1 H, m); MS (ion spray) (positive) m/z 361 $(M + Na)^+$; $[\alpha]^{26}_D = -19.4°$ (c = 2.4, $CHCl_3$).

(+)−(1*R*,1a*R*,1b*S*,4a*R*,5a*R*)-1-Fluoro-3,3-dioxotetrahydro-2,4-dioxa-3λ^6-thiacyclopropa[a]pentalene-1,1b-dicarboxylic Acid 2-Benzyl 6-Ethyl Ester (+)-19. In a manner similar to the preparation of (+)-**18** from (−)-**16**, (+)-**19** (1.15 g, 93 %) was obtained from (−)-**17** (1.05 g, 3.10 mmol) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.29 (3 H, t, J = 7.2 Hz), 2.53−2.61(1 H, m), 2.68−2.85 (3 H, m), 4.19−4.31(2 H, m), 5.26 (1 H, d, J = 12.1 Hz), 5.33 (1 H, d, J = 12.1 Hz), 5.43−5.48 (1 H, m), 7.28−7.43(5 H, m); MS (ion spray) (positive) m/z 423 $(M + Na)^+$; $[\alpha]^{30}_D = +31.3°$ (c = 0.20, $CHCl_3$).

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Azido-6-fluoro-3-hydroxybicyclo-[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (−)-20. A mixture of (+)-**18** (109 g, 0.322 mol) and NaN_3 (37.7 g, 0.580 mol) in a mixture of DMF (1.10 L) and H_2O (110 mL) was stirred for 14 h at 50 °C. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of ether (6.48 L) and H_2O (177 mL). Then 20% H_2SO_4 (516 mL) was added dropwise to the mixture with ice-cooling, and the mixture was vigorously stirred for 34 h at room temperature. The organic layer of the mixture was separated, washed with saturated brine, dried with $MgSO_4$, evaporated, and chromatographed (hexane/AcOEt = 4:1) to yield (−)-**20** (88.5 g, 91 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 1.33 (3 H, t, J = 7.0 Hz), 1.38 (3 H, t, J = 7.0 Hz), 2.25 (1 H, ddd, J = 8.2, 5.2, 3.4 Hz), 2.32 (1 H, dd, J = 8.2, 3.0 Hz), 2.40 (1 H, ddd, J = 13.4, 8.5, 5.2 Hz), 2.50 (1 H, dd, J = 13.4, 7.6 Hz), 2.65 (1 H, d, J = 6.7 Hz, D_2O changeable), 4.21−4.48 (5 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.05, 14.14, 28.97 (d, J = 11.4 Hz), 33.03, 33.83 (d, J = 10.4 Hz), 62.37, 62.67, 77.69, 77.80, 81.00 (d, J = 248.3 Hz),

168.14 (d, J = 24.8 Hz), 168.64; MS (ion spray) (positive) m/z 324 $(M + Na)^+$; $[\alpha]^{22}_D = -48.7°$ (c = 1.0, $CHCl_3$).

(+)−(1*S*,2*S*,3*S*,5*S*,6*S*)-2-Azido-6-fluoro-3-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (+)-20. In a manner similar to the preparation of (−)-**20** from (+)-**18**, (+)-**20** (3.94 g, 91%) was obtained from (−)-**18** (4.85 g, 14.3 mmol) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 1.33 (3 H, t, J = 7.0 Hz), 1.38 (3 H, t, J = 7.0 Hz), 2.25 (1 H, ddd, J = 8.2, 5.2, 3.4 Hz), 2.32 (1 H, dd, J = 8.2, 3.0 Hz), 2.40 (1 H, ddd, J = 13.4, 8.5, 5.2 Hz), 2.50 (1 H, dd, J = 13.4, 7.6 Hz), 2.65 (1 H, d, J = 6.7 Hz, D_2O changeable), 4.21−4.48 (5 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.05, 14.14, 28.97 (d, J = 11.4 Hz), 33.03, 33.83 (d, J = 10.4 Hz), 62.37, 62.67, 77.69, 77.80, 81.00 (d, J = 248.3 Hz), 168.14 (d, J = 24.8 Hz), 168.64; MS (ion spray) (positive) m/z 324 $(M + Na)^+$; $[\alpha]^{22}_D = +47.9°$ (c = 1.3, $CHCl_3$).

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Azido-6-fluoro-3-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic Acid 2-Benzyl 6-Ethyl Ester (−)-21. In a manner similar to the preparation of (−)-**20** from (+)-**18**, (−)-**21** (3.02 g, 89%) was obtained from (+)-**19** (3.73 g, 9.32 mmol) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.32 (3 H, t, J = 7.2 Hz), 2.18−2.54 (5 H, m), 4.22−4.36 (1 H, m), 4.26 (2 H, q, J = 7.2 Hz), 5.27 (1 H, d, J = 12.2 Hz), 5.35 (1 H, d, J = 12.2 Hz), 7.31−7.45 (5 H, m); MS (ion spray) (positive) m/z 386 $(M + Na)^+$; $[\alpha]^{30}_D = -50.2°$ (c = 1.0, $CHCl_3$).

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-6-fluoro-3-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (−)-11aa. A suspension of (−)-**21** (218 mg, 0.600 mmol) and 10% Pd/C (15 mg) in a mixture of AcOH (2.5 mL) and H_2O (0.5 mL) was stirred for 12 h under a hydrogen atmosphere at room temperature. After the Pd/C was filtered off through a Celite pad, the filtrate was concentrated under reduced pressure. The residue was dissolved in 10% HCl (7.8 mL), and the solution was heated at reflux for 1 h. The reaction mixture was concentrated under reduced pressure and chromatographed on AG50W-X8 cation-exchenge resin (Bio-Rad) (H_2O−50% aqueous THF−10% aqueous pyridine) to yield (−)-**11aa** (104 mg, 79%) as a white powder: mp >172 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.24−2.28 (2 H, m), 2.36−2.46 (1 H, m), 2.48−2.57 (1 H, m), 4.21−4.29 (1 H, m); MS (ion spray) (negative) m/z 218 $(M - 1)^+$; $[\alpha]^{25}_D = -27.0°$ (c = 0.20, H_2O). Anal. ($C_8H_{10}FNO_5$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Azido-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (−)-22be (Typical Procedure 1). To a suspension of NaH (60% in oil, 1.36 g, 33.9 mmol) in THF (46 mL) was added a solution of 3,4-dichlorobenzyl alcohol (60.1 g, 0.339 mol) in THF (68 mL), and the mixture was stirred for 0.5 h at room temperature. To the mixture was added trichloroacetonitrile (34.0 mL, 0.339 mol) with ice-cooling, and the resulting mixture was stirred for 2 h at room temperature. Pentane (45 mL) and methanol (1.1 mL) were added to the reaction mixture. After stirring for 30 min at room temperature, the precipitation that had formed was filtered off. The filtrate was concentrated under reduced pressure to yield crude 3,4-dichlorobenzyl-2,2,2-trichloroacetoimidate (107 g) as a brown viscous liquid.

To a mixture of the above crude 3,4-dichlorobenzyl-2,2,2-trichloroacetoimidate (75.2 g, 0.234 mol) and (−)-**20** (47.0 g, 0.156 mol) in a mixture of $CHCl_3$ (200 mL) and cyclohexane (400 mL) was added trifluoromethanesulfonic acid (8.28 mL) under a nitrogen atmosphere. After the mixture was stirred for 4.5 h at 30 °C, the precipitate that had formed was filtered off. Saturated aqueous $NaHCO_3$ was added to the filtrate with ice-cooling. The mixture was extracted with $CHCl_3$ (×2). The $CHCl_3$ layer was washed with saturated brine, dried with Na_2SO_4, concentrated under reduced pressure, and chromatographed (hexane/AcOEt = 15:1) to yield (−)-**22be** (30.2 g, 42%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.26−1.39 (6 H, m), 2.24−2.51 (4 H, m), 3.91−4.05 (1 H, m), 4.18−4.35 (4 H, m), 4.42 (1 H, d, J = 11.9 Hz), 4.64 (1 H, d, J = 11.9 Hz), 7.05−7.14 (1 H, m), 7.36−7.43 (2 H, m); MS (ion spray) (positive) m/z 482 $(M + Na)^+$; $[\alpha]^{24}_D = -14.5°$ (c = 0.94, $CHCl_3$).

(+)−(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (+)-24be (Typical Procedure 2). A solution of (−)-**22be** (27.5 g, 59.7 mmol) and Me_3P (1 M THF solution, 65.7 mL) in a mixture of THF (825 mL) and H_2O (82.5 mL) was stirred for 4 h at room temperature. Ether was added to the reaction mixture, and the organic layer of the mixture was separated. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated brine, dried with Na_2SO_4, evaporated, and chromatographed (hexane/AcOEt = 4:1−3:2) to yield (+)-**24be** (23.1 mg, 89%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.24−1.40 (6 H, m), 2.02−2.28 (2 H, m), 2.51−2.80 (2 H, m), 3.98−4.08 (1 H, m), 4.18−4.34 (4 H, m), 4.43 (1 H, d, J = 12.5 Hz), 4.53 (1 H, d, J = 12.5 Hz), 7.10−7.19 (1 H, m), 7.36−7.45 (2 H, m); MS (ion spray) (positive) m/z 456 $(M + Na)^+$; $[\alpha]^{22}_D = +11.6°$ (c = 0.50, $CHCl_3$).

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (−)-11be (Typical Procedure 3). A mixture of (+)-**24be** (22.9 g, 52.7 mmol) and a solution of $LiOH·H_2O$ (7.08 g, 169 mmol) in H_2O (240 mL) in THF (480 mL) was stirred for 8 days at room temperature. 1 N HCl (169 mL) was added to the reaction mixture and stirred for 14 h at room temperature. The precipitate was collected by filtration and washed with H_2O and THF to yield (−)-**11be** (12.3 g, 62%) as a white powder: mp >230 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.28−2.45 (3 H, m), 2.50 (1 H, dd, J = 7.6, 13.4 Hz), 4.05−4.11 (1 H, m), 4.52 (1 H, d, J = 12.1 Hz), 4.60 (1 H, d, J = 12.1 Hz), 7.26−7.58 (3 H, m); MS (ion spray) (negative) m/z 376 $(M - 1)^-$; $[\alpha]^{27}_D = -7.2°$ (c = 0.4, 1 M NaOH). Anal. ($C_{15}H_{14}Cl_2FNO_5$) C, H, N.

(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Azido-3-methoxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid 2-Benzyl 6-Ethyl Ester 23ab. To a solution of (−)-**21** (50 mg, 0.138 mmol) and 2,6-di-*tert*-butylpyridine (158 mg, 0.826 mmol) in CH_2Cl_2 (0.5 mL) was added methyl trifluoromethanesulfonate (113 mg, 0.689 mmol), and the resulting mixture was stirred for 4 days at room temperature. 1 N aqueous HCl was added to the reaction mixture, and extracted with ether (×3). The combined organic layer was washed with saturated brine, dried with $MgSO_4$, evaporated, and chromatographed (hexane/AcOEt = 9:1) to yield **23ab** (42 mg, 81%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, TMSP) δ 1.32 (3 H, t, J = 7.2 Hz), 2.20−2.50 (4 H, m), 3.32 (3 H, s), 3.78−3.86 (1 H, m), 4.26 (2 H, q, J = 7.2 Hz), 5.26 (1 H, d, J = 12.3 Hz), 5.34 (1 H, d, J = 12.3 Hz), 7.30−7.42 (5 H, m); MS (ion spray) (positive) m/z 400 $(M + Na)^+$.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-methoxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (−)-11ab. A suspension of **23ab** (280 mg, 0.742 mmol) and 10% Pd/C (28 mg) in a mixture of AcOH (4 mL) and H_2O (1 mL) was stirred for 18 h under a hydrogen atmosphere at room temperature. The Pd/C was filtered off through a Celite pad, and the filtrate was concentrated under reduced pressure to yield crude **26ab**. The residue was dissolved in 10% aqueous HCl (8 mL), and the solution was heated at reflux for 1.5 h. After cooling to room temperature, the solution was chromatographed on AG50W-X8 cation-exchange resin (Bio-Rad) (H_2O−50% aqueous THF−10% aqueous pyridine) to yield (−)-**11ab** (137 mg, 79%) as a white powder: mp >199 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.33−2.44 (3 H, m), 2.63 (1 H, dd, J = 7.9,13.1 Hz), 3.36 (3 H, s), 3.96 (1 H, dd, J = 7.1, 13.1 Hz); MS (ion spray) (negative) m/z 232 $(M - 1)^-$; $[\alpha]^{24}_D = -58.0°$ (c = 0.43, 1 M NaOH). Anal. ($C_9H_{12}FNO_5·0.3H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Azido-3-(2-propenyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid 2-Benzyl 6-Ethyl Ester (−)-23ac. In a manner similar to the preparation of (−)-**22be** from (−)-**20**, (−)-**23ac** (312 mg, 21%) was obtained from (−)-**21** (1.34 g, 3.68 mmol) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.32 (3 H, t), 2.16−2.51 (4 H, m), 3.87−4.15 (3 H, m), 4.27 (2 H, q, J = 7.0 Hz), 5.10−5.41 (4 H, m), 5.67−6.00 (1 H, m), 7.31−7.44 (5 H, m);

MS (ion spray) (positive) *m/z* 426 $(M + Na)^+$; $[\alpha]^{29}_D = -18.9°$ (c = 1.3, $CHCl_3$).

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(2-propenyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid 2-Benzyl 6-Ethyl Ester (−)-25ac. In a manner similar to the preparation of **(+)-24be** from (−)-**22be**, (−)-**25ac** (115 mg, 62%) was obtained from (−)-**23ac** (196 mg, 0.486 mmol) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.30 (3 H, t, J = 7.3 Hz), 2.06−2.52 (4 H, m), 3.64−3.82 (1 H, m), 3.92−4.14 (2 H, m), 4.24 (2 H, q, J = 7.3 Hz), 5.08−5.37 (4H, m), 5.66−5.85 (1 H, m), 7.30−7.48 (5 H, m); MS (ion spray) (positive) *m/z* 312 $(M + Na)^+$; $[\alpha]^{25}_D = -17.4°$ (c = 2.0, $CHCl_3$).

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(2-propenyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (−)-11ac. In a manner similar to the preparation of (−)-**11be** from (+)-**24be**, (−)-**11ac** (43 mg, 59%) was obtained from (−)-**25ac** (105 mg, 0.278 mmol) as a white powder: mp >248 °C (dec); ^{1}H NMR (200 MHz, D_2O, TMSP) δ 2.22−2.44 (3H, m), 2.58 (1 H, dd, J = 7.5, 13.6 Hz), 4.01−4.10 (3 H, m), 5.24 (1 H, d, J = 10.4 Hz), 5.31 (1 H, d, J = 17.3 Hz), 5.81−5.98 (1 H, m); MS (ion spray) (negative) *m/z* 258 $(M - 1)^-$; $[\alpha]^{29}_D = -34.1°$ (c = 1.0, 1 M NaOH). Anal. ($C_{11}H_{14}FNO_5 \cdot 0.1H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-propoxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (−)-11ad. A suspension of (−)-**11ac** (40 mg, 0.154 mmol) and 10% Pd/C (4 mg) in H_2O (1 mL) was stirred under a hydrogen atmosphere at room temperature for 2 days. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure and chromatographed on AG50W-X8 cation-exchange resin (Bio-Rad) (H_2O−50% aqueous THF−10% aqueous pyridine) to yield (−)-**11ad** (30 mg, 73%) as a white powder: mp >165 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 0.85 (3 H, t, J = 7.5 Hz), 1.43−1.64 (2 H, m), 2.22−2.30 (2 H, m), 2.34−2.47 (1 H, m), 2.58 (1 H, dd, J = 7.8, 13.5 Hz), 3.38−3.60 (2 H, m), 3.99−4.08 (1 H, m); MS (ion spray) (negative) *m/z* 260 $(M - 1)^-$; $[\alpha]^{30}_D = -34.6°$ (c = 0.79, 1 M NaOH). Anal. ($C_{11}H_{16}FNO_5 \cdot 0.1Py$)[42] C, H, N.

(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Azido-3-(1-methylbut-2-enyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester 22ae. In a manner similar to the preparation of (−)-**22be** from (−)-**20**, a mixture of diastereomer **22ae** (79 mg, 20%) was obtained from (−)-**20** (320 mg, 1.06 mmol) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.13 (3 H, t, J = 6.6 Hz), 1.27−1.42 (6 H, m), 1.69 (3 H, d, J = 6.4), 2.20−2.48 (4 H, m), 3.78−4.45 (6 H, m), 5.13−5.37 (1 H, m) 5.52−5.74 (1 H, m); MS (ion spray) (positive) *m/z* 392 $(M + Na)^+$.

(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(1-methylbutyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester 24ae. A suspension of **22ae** (75 mg, 0.203 mmol) and 10% Pd/C (10 mg) in a mixture of AcOH (4.7 mL) and H_2O (1.6 mL) was stirred under a hydrogen atmosphere for 22 h at room temperature. The reaction mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure and chromatographed (hexane/AcOEt = 2:1) to yield a mixture of diastereomer **24ae** (47 mg, 68%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 0.82−0.94 (3 H, m), 1.02−1.10 (3 H, m), 1.16−1.46 (10 H, m), 2.06−2.44 (4 H, m), 3.32−3.78 (2 H, m), 4.12−4.40 (4 H, m); MS (ion spray) (positive) *m/z* 346 $(M + 1)^+$.

(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-((*RS*)-1-methylbutyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid 11ae. In a manner similar to the preparation of (−)-**11be** from **24be**, a mixture of diastereomer **11ae** (32 mg, 85%) was obtained from **25ae** (45 mg, 0.131 mmol) as a white powder: mp >170 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 0.80−0.94 (3 H, m), 1.06−1.16 (3 H, m), 1.20−1.42 (3 H, m), 1.42−1.58 (1 H, m), 2.18−2.30 (2 H, m), 2.32−2.48 (1 H, m), 2.48−2.60 (1 H, m), 3.43−3.63 (1 H, m), 4.03−4.18 (1 H, m); MS (ion spray) (negative) *m/z* 288 $(M - 1)^-$. Anal. ($C_{13}H_{20}FNO_5 \cdot 0.3H_2O$) C, H, N.

(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Azido-3-(2-cyclopentenyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid 2-Benzyl 6-Ethyl Ester 23af. In a manner similar to the preparation of (−)-**22be** from (−)-**20**, a mixture of diastereomer **23af** (339 mg, 72%) was obtained from (−)-**20** (650 mg, 1.79 mmol) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.32 (3 H, t, J = 7.3 Hz), 1.90−2.52 (8 H, m), 3.94−4.14 (1 H, m), 4.27 (2 H, q, J = 7.3 Hz), 4.52−4.79 (1 H, m), 5.15−5.41 (2 H, m), 5.58−5.82 (1 H, m), 5.88−6.04 (1 H, m), 7.30−7.46 (5 H, m); MS (ion spray) (positive) *m/z* 452 $(M + Na)^+$.

(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-cyclopentyloxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid 6-Ethyl Ester 26af. A suspension of **23af** (331 mg, 0.771 mmol) and 10% Pd/C (39 mg) in a mixture of AcOH (18 mL) and H_2O (6 mL) was stirred under a hydrogen atmosphere for 31 h at room temperature. The reaction mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure to yield **26af** (250 mg). Compound **26af** was used for the next reaction without any purification.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-cyclopentyloxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (−)-11af. In a manner similar to the preparation of (−)-**11be** from (+)-**24be**, (−)-**11af** (61 mg, 28% form **23af**) was obtained from **26af** (250 mg) as a white powder: mp >170 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 1.38−1.84 (8 H, m), 2.22−2.30 (2 H, m), 2.32−2.44 (1 H, m), 2.54 (1 H, dd, J = 8.0, 13.6 Hz), 3.97−4.13 (2 H, m); MS (ion spray) (negative) *m/z* 286 $(M - 1)^-$; $[\alpha]^{26}_D = -24.9°$ (c = 0.33, 1 M NaOH). Anal. ($C_{13}H_{18}FNO_5 \cdot 0.2Py$)[42] C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Azido-3-(3-phenylpropoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (−)-22ah. In a manner similar to the preparation of **23ab** from (−)-**21**, (−)-**22ah** (125 mg, 70%) was obtained from (−)-**20** (128 mg, 0.425 mmol) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.33 (3 H, t, J = 7.0 Hz), 1.36 (3 H, t, J = 7.0 Hz), 1.73−1.88 (2 H, m), 2.25−2.66 (6 H, m), 3.37−3.65 (2 H, m), 3.85−3.96 (1 H, m), 4.21−4.44 (4 H, m), 7.12−7.34 (5 H, m); MS (ion spray) (positive) *m/z* 442 $(M + Na)^+$; $[\alpha]^{26}_D = -33.6°$ (c = 0.70, $CHCl_3$).

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-phenylpropoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (−)-24ah. A suspension of (−)-**22ah** (120 mg, 0.286 mmol) and 10% Pd/C (11 mg) in a mixture of AcOH (6.6 mL) and H_2O (2.2 mL) was stirred under hydrogen atmosphere for 14 h at room temperature. The reaction mixture was filtrated through a Celite pad. The filtrate was concentrated under reduced pressure and chromatographed (hexane/AcOEt = 3:2) to yield (−)-**24ah** (106 mg, 93%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.25−1.39 (6 H, m), 1.72−2.70 (8 H, m), 3.34−3.70 (3 H, m), 4.14−4.44 (4 H, m), 7.12−7.34 (5 H, m); MS (ion spray) (positive) *m/z* 416 $(M + Na)^+$; $[\alpha]^{24}_D = -16.0°$ (c = 0.47, $CHCl_3$).

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-phenylpropoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (−)-11ah. In a manner similar to the preparation of (−)-**11be** from (+)-**24be**, (−)-**11ah** (61 mg, 68%) was obtained from (−)-**24ah** (105 mg, 0.270 mmol) as a white powder: mp >230 °C (dec); ^{1}H NMR (300 MHz, D_2O) δ 1.78−1.93 (2 H, m), 2.23−2.30 (2 H, m), 2.31−2.46 (1 H, m), 2.54 (1 H, dd, J = 7.39, 13.4 Hz), 2.61−2.72 (1 H, m), 3.40−3.61 (2H, m), 3.94−4.05 (1 H, m), 7.22−7.43 (5 H, m); MS (ion spray) (negative) *m/z* 336 $(M - 1)^-$; $[\alpha]^{26}_D = -43.4°$ (c = 0.14, 1 M NaOH). Anal. ($C_{17}H_{20}FNO_5 \cdot 0.2H_2O$) C, H, N.

(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Azido-3-(3-nitrobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester 22aw. In a manner similar to the preparation of (−)-**22be** from (−)-**20**, **22aw** (240 mg) was obtained from (−)-**20** (350 mg, 1.16 mmol) as a colorless oil. Compound **22aw** included an impurity and was used for the next reaction without further purification.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-nitrobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (−)-24aw. In a manner similar to the preparation of (+)-**24be** from (−)-**22be**, (−)-**24aw** (100 mg, 21% (form (−)-**20**)) was obtained from **22aw** (238 mg) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.31 (3 H, t, J = 7.0 Hz), 1.32 (3 H, t, J = 7.0 Hz), 2.14−2.32 (2 H, m), 2.42−2.54 (2 H, m), 3.74−3.92 (1 H, m), 4.26 (2 H, q, J = 7.0 Hz), 4.17−4.46 (2 H,

m), 4.62 (1 H, d, J = 12.3 Hz), 4.81 (1 H, d, J = 12.3 Hz), 7.44−7.64 (2 H, m), 8.09−8.20 (2 H, m); MS (ion spray) (positive) m/z 433 $(M + Na)^+$; $[\alpha]^{26}_D = -5.1°$ (c = 0.49, $CHCl_3$).

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-aminobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (−)-24ax. A mixture of (−)-**24aw** (127 mg, 0.31 mmol) and Zn powder (101 mg, 1.55 mmol) in AcOH (0.21 mL) was stirred for 3 h at room temperature. The reaction mixture was filtered, and the solid was washed with H_2O and AcOEt. The filtrates were combined and extracted with AcOEt. The combined extract was washed with 0.5 M Na_2CO_3 and H_2O, dried with Na_2SO_4, and then chromatographed ($CHCl_3$/EtOH = 30:1) to yield (−)-**24ax** (96 mg, 81%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.30 (6 H, t, J = 7.1 Hz), 2.04−2.28 (2 H, m), 2.32−2.50 (2 H, m), 3.68−3.82 (1 H, m), 4.14−4.38 (4 H, m), 4.44 (1 H, d, J = 11.8 Hz), 4.55 (1 H, d, J = 11.8 Hz), 6.53−6.70 (3 H, m), 7.02−7.18 (1 H, m); MS (ion spray) (positive) m/z 403 $(M + Na)^+$; $[\alpha]^{23}_D = -27.0°$ (c = 0.26, $CHCl_3$).

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-aminobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (−)-11ax. In a manner similar to the preparation of (−)-**11be** from (+)-**24be**, (−)-**11ax** (60 mg, 77%) was obtained from (−)-**24ax** (90 mg, 0.24 mmol) as a white powder: mp >190 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.23−2.32 (2 H, m), 2.34−2.60 (2 H, m), 4.05−4.13 (1 H, m), 4.48−4.66 (2 H, m), 7.00−7.14 (3 H, m), 7.32−7.41 (1 H, m); MS (ion spray) (negative) m/z 323 $(M - 1)^-$; $[\alpha]^{28}_D = -19.1°$ (c = 0.26, H_2O). Anal. ($C_{15}H_{17}FN_2O_5 \cdot 3.4H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Azido-6-fluoro-3-trifluoromethanesulfonyloxybicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (−)-27. A solution of trifluoromethanesulfonyl anhydride (117 μL) in CH_2Cl_2 (0.6 mL) was added to a solution of (−)-**20** (120 mg, 0.398 mmol) and pyridine (72 μL) in CH_2Cl_2 (2.0 mL) under a nitrogen atmosphere at −75 °C. After the mixture was stirred for 2 h with ice-cooling, ether (10 mL) was added to the reaction mixture. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure and chromatographed (hexane/AcOEt = 5:1) to yield (−)-**27** (166 mg, 96%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.35 (3 H, t, J = 7.0 Hz), 1.38 (3 H, t, J = 7.0 Hz), 2.35−2.50 (2 H, m), 2.62−2.86 (2 H, m), 4.31 (2 H, q, J = 7.0 Hz), 4.27−4.55 (2 H, m), 4.94−5.10 (1 H, m); MS (FAB) (positive) m/z 434 $(M + 1)^+$; $[\alpha]^{26}_D = -31.2°$ (c = 0.43, $CHCl_3$).

(+)−(1*R*,2*R*,3*S*,5*R*,6*R*)-2-Azido-6-fluoro-3-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (+)-28. A mixture of (−)-**27** (701 mg, 1.62 mmol), KNO_2 (688 mg, 8.09 mmol), and 18-crown-6 (428 mg, 1.62 mmol) in DMF (6.9 mL) was stirred at 45 °C under a nitrogen atmosphere for 5 days. H_2O was added to the reaction mixture, and the mixture was extracted with AcOEt (×2). The combined extract was washed with saturated brine, dried with Na_2SO_4, evaporated, and chromatographed (hexane/AcOEt = 5:1) to yield (+)-**28** (388 mg, 80%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 1.34 (3 H, t, J = 7.0 Hz), 1.36 (3 H, t, J = 7.0 Hz), 2.15 (1 H, ddd, J = 14.9, 2.7, 0.6 Hz), 2.21−2.25 (1 H, m), 2.43 (1 H, dd, J = 8.3, 3.4 Hz), 2.61 Hz (1 H, dd, J = 16.2, 12.2 Hz, D_2O changeable), 2.85−2.92 (1 H, m), 4.29 (2 H, q, J = 7.0 Hz), 4.31−4.38 (2 H, m), 4.52−4.57 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.11, 14.13, 30.16 (d, J = 11.3 Hz), 35.58, 35.56, 36.94 (d, J = 10.3 Hz), 62.52, 62.95. 76.49, 76.83, 81.16 (d, J = 244.1 Hz), 167.71 (d, J = 25.8 Hz), 170.56; MS (ion spray) (positive) m/z 324 $(M + Na)^+$; $[\alpha]^{25}_D = +6.4°$ (c = 0.96, $CHCl_3$).

(+)−(1*R*,2*R*,3*S*,5*R*,6*R*)-2-Amino-6-fluoro-3-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (+)-29a. A suspension of (+)-**28** (100 mg, 0.332 mmol) and 10% Pd/C (12 mg) in a mixture of AcOH (7.7 mL) and H_2O (2.6 mL) was stirred under a hydrogen atmosphere for 20 h at room temperature. The Pd/C was filtered off through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was chromatographed ($CHCl_3$/EtOH = 35:1) to yield (+)-**29a** (91 mg, 100%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.32 (6 H, t, J = 7.25 Hz) 2.07−0.23 (2 H, m) 2.37−2.46 (1 H, m) 2.73−2.89 (1 H, m) 4.11−4.38 (5 H, m); MS (ion spray) (positive) m/z 276 $(M + 1)^+$; $[\alpha]^{30}_D = +2.4°$ (c = 0.30, $CHCl_3$).

(−)-(1*R*,2*R*,3*S*,5*R*,6*R*)-2-Amino-6-fluoro-3-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (−)-12a. In a manner similar to the preparation of (−)-**11be** from (+)-**24be**, (−)-**12a** (35 mg, 48%) was obtained from (+)-**29a** (91 mg, 0.332 mmol) as a white powder: mp >181 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 1.98−2.09 (1 H, m) 2.20−2.40 (2 H, m) 2.81−2.99 (1 H, m) 4.58−4.70 (1 H, m); MS (negative) m/z 218 $(M - 1)^-$; $[\alpha]^{27}_D = -58.0°$ (c = 0.17, 1 M NaOH). Anal. ($C_8H_{10}FNO_5$) C, H, N.

(−)-(1*R*,2*R*,3*S*,5*R*,6*R*)-2-Azido-6-fluoro-3-methoxybicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (−)-29b. In a manner similar to the preparation of **23ab** from (−)-**21**, (−)-**29b** (41 mg, 43%) was obtained from (+)-**28** (90 mg, 0.299 mmol) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.33 (3 H, t, J = 7.3 Hz), 1.38 (3 H, t, J = 7.3 Hz), 2.07−2.24 (2 H, m), 2.35−2.42 (1 H, m), 2.56−2.73 (1H, m), 3.40 (3 H, s), 4.23−4.40 (5 H, m); MS (ion spray) (positive) m/z 388 $(M + Na)^+$; $[\alpha]^{28}_D = -58.2°$ (c = 0.35, $CHCl_3$).

(−)-(1*R*,2*R*,3*S*,5*R*,6*R*)-2-Amino-6-fluoro-3-methoxybicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Diethyl Ester (−)-30b. In a manner similar to the preparation of (−)-**24ah** from (−)-**22ah**, (−)-**30b** (33 mg, 88%) was obtained from (−)-**29b** (41 mg, 0.130 mmol) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.30 (3 H, t, J = 7.3 Hz), 1.33 (3 H, t, J = 7.30 Hz), 2.06−2.18 (2 H, m), 2.43−2.49 (1 H, m), 2.56−2.77 (1 H, m), 3.33 (s, 3 H), 3.81 (1 H, dd, J = 9.0, 3.7 Hz), 4.24 (2 H, q, J = 7.3 Hz), 4.28 (2 H, q, J = 7.30 Hz); MS (ion spray) (positive) m/z 312 $(M + Na)^+$; $[\alpha]^{26}_D = -18.3°$ (c = 0.36, $CHCl_3$).

(−)-(1*R*,2*R*,3*S*,5*R*,6*R*)-2-Amino-6-fluoro-3-methoxybicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (−)-12b. In a manner similar to the preparation of (−)-**11be** from **24be**, **12b** (24 mg, 90%) was obtained from (−)-**30b** (33 mg, 0.114 mmol) as a white powder: mp >171 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.04−2.15 (1 H, m), 2.27−2.38 (1 H, m), 2.39−2.47 (1 H, m), 2.76−2.93 (1 H, m), 3.35 (3 H, s), 4.28−4.38 (1 H, m); MS (negative) m/z 232 $(M - 1)^-$; $[\alpha]^{21}_D = -49.7°$ (c = 0.20, 1 M NaOH). Anal. ($C_9H_{12}FNO_5 \cdot 0.2H_2O$) C, H, N.

According to typical procedures 1, 2, and 3, the optically active compounds **11ag**, **11ai**−**11aw**, **11ay**−**11cc**, **12c**, and **12d** were synthesized from (−)- and (+)-**20**, (−)-**21**, and (+)-**28**.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-benzyloxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11ag: a white powder; mp >226 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.24−2.57 (4 H, m), 4.04−4.14 (1 H, m), 4.56 (1 H, d, J = 11.5 Hz), 4.62 (1 H, d, J = 11.5 Hz), 7.41 (5 H, s); MS (negative) m/z 308 $(M - 1)^-$; $[\alpha]^{26}_D = -24.3°$ (c = 0.22, 1 M NaOH). Anal. ($C_{15}H_{16}FNO_5 \cdot 0.3H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(4-fluorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11ai: a white powder; mp >239 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.29−2.54 (4 H, m), 4.07−4.14 (1 H, m), 4.53 (1 H, d, J = 11.5 Hz), 4.60 (1 H, d, J = 11.5 Hz), 7.11−7.18 (2 H, m), 7.37−7.42 (2 H, m); MS (negative) m/z 326 $(M - 1)^-$; $[\alpha]^{29}_D = -18.9°$ (c = 0.61, 1 M NaOH). Anal. ($C_{15}H_{15}F_2NO_5$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(2-chlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (−)-11aj: a white powder; mp >195 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.22−2.49 (3 H, m), 2.57 (1 H, dd, J = 7.5, 13.5 Hz), 4.15−4.21 (1 H, m), 4.66−4.82 (2 H, m), 7.33−7.50 (4 H, m); MS (negative) m/z 324 $(M - 1)^-$; $[\alpha]^{25}_D = -42.4°$ (c = 0.15, 1 M NaOH). Anal. ($C_{15}H_{15}ClFNO_5 \cdot 1.3H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-chlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11ak: a white powder; mp >220 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.23−2.56 (4 H, m), 4.06−4.13 (1 H, m), 4.55 (1 H, d, J = 12.1 Hz), 4.63 (1 H, d, J = 12.1 Hz), 7.31−7.44 (4 H, m); MS (negative) m/z 324 $(M - 1)^-$; $[\alpha]^{27}_D = -12.5°$ (c = 0.63, 1 M NaOH). Anal. ($C_{15}H_{15}ClFNO_5 \cdot 0.3H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(4-chlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (−)-

11al: a white powder; mp >220 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.29−2.54 (4 H, m), 4.05−4.12 (1 H, m), 4.54 (1 H, d, J = 11.7 Hz), 4.61 (1 H, d, J = 11.7 Hz), 7.35−7.44 (4 H, m); MS (negative) m/z 324 (M − 1)$^-$; $[\alpha]^{29}_D$ = −8.0° (c = 0.53, 1 M NaOH). Anal. ($C_{15}H_{15}ClFNO_5 \cdot 0.2H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-bromobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11am: a white powder; mp >250 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.20−2.48 (3 H, m), 2.51 (1 H, dd, J = 7.5, 13.5 Hz), 4.04−4.12 (1 H, m), 4.54 (1 H, d, J = 12.1 Hz), 4.61 (1 H, d, J = 12.1 Hz), 7.30−7.59 (4 H, m); FAB (negative) m/z 386 (M − 1)$^-$; $[\alpha]^{29}_D$ = −11.7° (c = 0.33, 1 M NaOH). Anal. ($C_{15}H_{15}BrFNO_5 \cdot 0.2H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-methylbenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11an: a white powder; mp >215 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.24−2.27 (2 H, m), 2.35 (3 H, s), 2.37−2.54 (2 H, m), 4.08 (1 H, dd, J = 7.6, 12.7 Hz), 4.52 (1 H, d, J = 11.5 Hz), 4.59 (1 H, d, J = 11.5 Hz), 7.20−7.36 (4 H, m); MS (negative) m/z 322 (M − 1)$^-$; $[\alpha]^{29}_D$ = −21.3° (c = 0.47, 1 M NaOH). Anal. ($C_{16}H_{18}FNO_5 \cdot 0.5H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-trifluoromethylbenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11ao: a white powder; mp >220 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.28−2.54 (4 H, m), 4.08−4.15 (1 H, m), 4.62 (1 H, d, J = 12.1 Hz), 4.70 (1 H, d, J = 12.1 Hz), 7.55−7.71 (4 H, m); MS (negative) m/z 376 (M − 1)$^-$; $[\alpha]^{27}_D$ = −12.6° (c = 0.57, 1 M NaOH). Anal. ($C_{16}H_{15}F_4NO_5 \cdot 0.5H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-cyanobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11ap: a white powder; mp >184 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.26−2.54 (4 H, m), 4.09−4.13 (1 H, m), 4.59 (1 H, d, J = 12.0 Hz), 4.46 (1 H, d, J = 12.0 Hz), 7.50 (1 H, dd, J = 7.9, 7.9 Hz), 7.68 (1 H, d, J = 7.9 Hz), 7.73 (1 H, d, J = 7.9 Hz), 7.76 (1 H, s); MS (negative) m/z 333 (M − 1)$^-$; $[\alpha]^{28}_D$ = −11.8° (c = 0.32, 1 M NaOH). Anal. ($C_{16}H_{15}FN_2O_5 \cdot 0.8H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-hydroxycarbonylbenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11aq: a white powder; mp >195 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.25−2.34 (2 H, m), 2.36−2.40 (2 H, m), 4.04−4.18 (1 H, m), 4.57−4.73 (2 H, m), 7.40−7.64 (2 H, m), 7.83−7.93 (2 H, m); MS (negative) m/z 352 (M − 1)$^-$; $[\alpha]^{26}_D$ = −13.6° (c = 0.23, 1 M NaOH). Anal. ($C_{16}H_{16}FNO_7 \cdot 1H_2O \cdot 0.1Py$)[42] C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(2-phenylbenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11ar: a white powder; mp >180 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.20−2.27 (4 H, m), 3.84−3.90 (1 H, m), 4.46 (1 H, d, J = 11.0 Hz), 4.55 (1 H, d, J = 11.0 Hz), 7.34−7.58 (9 H, m); MS (negative) m/z 384 (M − 1)$^-$; $[\alpha]^{26}_D$ = −25.6° (c = 0.16, 1 M NaOH). Anal. ($C_{21}H_{20}FNO_5 \cdot 0.2H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-phenylbenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 11as: a white powder; mp >180 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.27−2.57 (4 H, m), 4.06−4.19 (1 H, m), 4.60−4.76 (2 H, m), 7.41−7.74 (9 H, m); MS (negative) m/z 384 (M − 1)$^-$; $[\alpha]^{27}_D$ = −12.3° (c = 0.14, 1 M NaOH). Anal. ($C_{21}H_{20}FNO_5 \cdot 0.5H_2O$) C, H, N.

(+)−(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(4-phenylbenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (+)-11at: a white powder; mp >215 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.23−2.60 (4 H, m), 4.03−4.15 (1 H, m), 4.60 − 4.74 (2 H, m), 7.40−7.77 (9 H, m); MS (negative) m/z 384 (M − 1)$^-$; $[\alpha]^{26}_D$ = +6.9° (c = 0.34, 1 M NaOH). Anal. ($C_{21}H_{20}FNO_5 \cdot 0.2H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-methoxybenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11au: a white powder; mp >165 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.24−2.46 (3 H, m), 2.51 (1 H, dd, J = 7.5, 13.6 Hz), 3.85 (3 H, s), 4.09 (1 H, dt, J = 5.0, 7.5 Hz), 4.54 (1 H, d, J = 11.7 Hz), 4.61 (1 H, d, J = 11.7 Hz), 6.95−7.15 (3 H, m), 7.38 (1 H, t, J = 8.1 Hz); MS (negative) m/z 338 (M − 1)$^-$; $[\alpha]^{24}_D$ = −8.4° (c = 0.07, 1 M NaOH). Anal. ($C_{16}H_{18}FNO_6 \cdot 0.2H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-phenoxybenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11av: a white powder; mp >180 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.26−2.49 (4 H, m), 4.03−4.09 (1 H, m), 4.53 (1 H, d, J = 12.0 Hz), 4.61 (1 H, d, J = 12.0 Hz), 7.05−7.26 (6 H, m), 7.40−7.48 (3 H, m); MS (negative) m/z 400 (M − 1)$^-$; $[\alpha]^{27}_D$ = −9.4° (c = 0.36, 1 M NaOH). Anal. ($C_{21}H_{20}FNO_6 \cdot 0.5H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-nitrobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11aw: a white powder; mp >234 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.24−2.34 (2 H, m), 2.36−2.62 (2 H, m), 4.08−4.20 (1 H, m), 4.64−4.80 (2 H, m), 7.64−7.68 (1 H, m), 7.76−7.84 (1 H, m), 8.18−8.28 (2 H, m); MS (negative) m/z 353 (M − 1)$^-$; $[\alpha]^{26}_D$ = −14.1° (c = 0.24, 1 M NaOH). Anal. ($C_{15}H_{15}FN_2O_7 \cdot 0.1H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3,4-difluorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11ay: a white powder; mp >220 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.25−2.46 (3 H, m), 2.51 (1 H, dd, J = 7.8, 12.8 Hz), 4.10 (1 H, dd, J = 6.6, 12.8 Hz), 4.52 (1 H, d, J = 11.7 Hz), 4.59 (1 H, d, J = 11.7 Hz), 7.16−7.32 (3 H, m); MS (negative) m/z 344 (M − 1)$^-$; $[\alpha]^{27}_D$ = −16.0° (c = 1.07, 1 M NaOH). Anal. ($C_{15}H_{14}F_3NO_5 \cdot 0.4H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3,5-difluorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11az: a white powder; mp >185 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.22−2.58 (4 H, m), 4.07−4.14 (1 H, m), 4.55 (1 H, d, J = 12.7 Hz), 4.62 (1 H, d, J = 12.7 Hz), 6.87−7.01 (3 H, m); MS (negative) m/z 344 (M − 1)$^-$; $[\alpha]^{27}_D$ = −14.4° (c = 1.08, 1 M NaOH). Anal. ($C_{15}H_{14}F_3NO_5 \cdot 0.8H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(2,3-difluorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11ba: a white powder; mp >180 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.29−2.56 (4 H, m), 4.09−4.16 (1 H, m), 4.63−4.76 (2 H, m), 7.14−7.31 (3 H, m); MS (negative) m/z 344 (M − 1)$^-$; $[\alpha]^{26}_D$ = −18.9° (c = 0.21, 1 M NaOH). Anal. ($C_{15}H_{14}F_3NO_5 \cdot 1.5H_2O \cdot 0.1Py$)[42] C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(2,4-difluorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bb: a white powder; mp >170 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.22−2.55 (4 H, m), 4.10−4.17 (1 H, m), 4.60 (1 H, d, J = 11.7 Hz), 4.65 (1 H, d, J = 11.7 Hz), 6.94−7.02 (2 H, m), 7.40−7.48 (1 H, m); MS (negative) m/z 344 (M − 1)$^-$; $[\alpha]^{27}_D$ = −8.7° (c = 0.48, 1 M NaOH). Anal. ($C_{15}H_{14}F_3NO_5 \cdot 1.5H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(2,5-difluorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bc: a white powder; mp >200 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.22−2.57 (4 H, m), 4.09−4.15 (1 H, m), 4.52−4.74 (2 H, m), 7.07−7.24 (3 H, m); MS (negative) m/z 344 (M − 1)$^-$; $[\alpha]^{26}_D$ = −22.7° (c = 0.24, 1 M NaOH). Anal. ($C_{15}H_{14}F_3NO_5 \cdot 0.2H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(2,6-difluorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bd: a white powder; mp >180 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.27−2.53 (4 H, m), 4.08−4.15 (1 H, m), 4.64−4.77 (2 H, m), 6.98−7.07 (2 H, m), 7.37−7.47 (1 H, m); MS (negative) m/z 344 (M − 1)$^-$; $[\alpha]^{26}_D$ = −5.1° (c = 0.26, 1 M NaOH). Anal. ($C_{15}H_{14}F_3NO_5 \cdot 1H_2O$) C, H, N.

(+)−(1*S*,2*S*,3*S*,5*S*,6S)-2-Amino-3-(3,4-dichloro-benzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (+)-11be: a white powder; mp >220 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.28−2.45 (3 H, m), 2.50 (1 H, dd, J = 7.6, 13.4 Hz), 4.05−4.11 (1 H, m), 4.52 (1 H, d, J = 12.1 Hz), 4.60 (1 H, d, J = 12.1 Hz), 7.26−7.58 (3 H, m); MS (ion spray) (negative) m/z 376 (M − 1)$^-$; $[\alpha]^{27}_D$ = +6.37° (c = 1.20, 1 M NaOH). Anal. ($C_{15}H_{14}Cl_2FNO_5$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3,5-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bf: a white powder; mp >180 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.22−2.55 (4 H, m), 4.05−4.12 (1 H, m),

4.52 (1 H, d, J = 12.4 Hz), 4.60 (1 H, d, J = 12.4 Hz), 7.34−7.44 (3 H, m); MS (negative) m/z 376 (M − 1)$^-$; $[\alpha]^{27}_D = -9.4°$ (c = 0.38, 1 M NaOH). Anal. ($C_{15}H_{14}Cl_2FNO_5 \cdot 0.8\ H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(2,3-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bg: a white powder; mp >210 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.28−2.62 (4 H, m), 4.13−4.23 (1 H, m), 4.70−4.85 (2 H, m), 7.31−7.56 (3 H, m); MS (negative) m/z 376 (M − 1)$^-$; $[\alpha]^{25}_D = -37.8°$ (c = 0.40, 1 M NaOH). Anal. ($C_{15}H_{14}Cl_2FNO_5 \cdot 0.1H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(2,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bh: a white powder; mp >215 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.28−2.60 (4 H, m), 4.13−4.19 (1 H, m), 4.62−4.84 (2 H, m), 7.37−7.54 (3 H, m); MS (negative) m/z 376 (M − 1)$^-$; $[\alpha]^{24}_D = -21.1°$ (c = 0.25, 1 M NaOH). Anal. ($C_{15}H_{14}Cl_2FNO_5$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(2,5-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bi: a white powder; mp >195 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.22−2.62 (4 H, m), 4.15−4.20 (1 H, m), 4.62−4.85 (2 H, m), 7.32−7.56 (3 H, m); MS (negative) m/z 376 (M − 1)$^-$; $[\alpha]^{26}_D = -22.0°$ (c = 0.27, 1 M NaOH). Anal. ($C_{15}H_{14}Cl_2FNO_5 \cdot 0.5H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(2,6-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bj: a white powder; mp >195 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.22−2.59 (4 H, m), 4.17−4.24 (1 H, m), 4.76−4.85 (2 H, m), 4.96 (1 H, d, J = 10.9 Hz), 7.29−7.48 (3 H, m); MS (negative) m/z 376 (M − 1)$^-$; $[\alpha]^{26}_D = -18.9°$ (c = 0.42, 1 M NaOH). Anal. ($C_{15}H_{14}Cl_2FNO_5 \cdot 0.5H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(4-chloro-3-fluorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bk: a white powder; mp >276 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.22−2.45 (3 H, m), 2.51 (1 H, dd, J = 7.6, 13.4 Hz), 4.02−4.20 (1 H, m), 4.54 (1 H, d, J = 12.1 Hz), 4.61 (1 H, d, J = 12.1 Hz), 7.13−7.20 (1 H, m), 7.22−7.30 (1 H, m), 7.44−7.53 (1 H, m); MS (negative) m/z 360 (M − 1)$^-$; $[\alpha]^{27}_D = -8.7°$ (c = 0.43, 1 M NaOH). Anal. ($C_{15}H_{14}ClF_2NO_5 \cdot 0.3H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3-chloro-4-fluorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bl: a white powder; mp >174 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.23−2.30 (2 H, m), 2.33−2.46 (1 H, m), 2.53 (1 H, dd, J = 7.8, 13.7 Hz), 4.06−4.18 (1 H, m), 4.62−4.73 (2 H, m), 7.16−7.23 (1 H, m), 7.35−7.43 (1 H, m), 7.45−7.53 (1 H, m); MS (negative) m/z 360 (M − 1)$^-$; $[\alpha]^{25}_D = -17.6°$ (c = 0.45, 1 M NaOH). Anal. ($C_{15}H_{14}ClF_2NO_5 \cdot 0.1H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(3,4,5-trichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bm: a white powder; mp >189 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.28−2.29 (2 H, m), 2.36−2.43 (1 H, m), 2.50 (1 H, dd, J = 13.4, 7.3 Hz), 4.05−4.11 (1 H, m), 4.51 (1 H, d, J = 13.4 Hz), 4.59 (1 H, d, J = 13.4 Hz), 7.51 (2 H, s); MS (negative) m/z 410 (M − 1)$^-$; $[\alpha]^{29}_D = -4.1°$ (c = 0.39, 1 M NaOH). Anal. ($C_{15}H_{13}Cl_3FNO_5 \cdot 0.1H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(2,3,4,5,6-pentafluorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bn: a white powder; mp >250 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.22−2.58 (4 H, m), 4.07−4.14 (1 H, m), 4.64−4.82 (2 H, m); MS (negative) m/z 398 (M − 1)$^-$; $[\alpha]^{28}_D = -5.2°$ (c = 0.42, 1 M NaOH). Anal. ($C_{15}H_{11}F_6NO_5 \cdot 0.3H_2O$) C, H, N.

(+)−(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-((*R)-1-(3,4-dichlorophenyl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (+)-11bo:** a white powder; mp >186 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 1.36 (3 H, d, J = 6.1 Hz), 2.10−2.39 (4 H, m), 3.84−3.97 (1 H, m), 4.59 (1 H, q, J = 6.1 Hz), 7.24 (1 H, d, J = 7.2 Hz), 7.53 (1 H, s), 7.55 (1 H, d, J = 7.2 Hz); MS (negative) m/z 390 (M − 1)$^-$; $[\alpha]^{27}_D = +94.2°$ (c = 0.95, 1 M NaOH). Anal. ($C_{16}H_{16}Cl_2FNO_5 \cdot 0.2Py$)[42] C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-((*S)-1-(3,4-dichlorophenyl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bp:** a white powder; mp >167 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 1.38 (3 H, d, J = 6.4 Hz), 2.21 (1 H, dd, J = 2.7, 7.8 Hz), 2.24−2.32 (1 H, m), 2.39−2.59 (2 H, m), 3.73−3.86 (1 H, m), 4.54 (1 H, q, J = 6.4 Hz), 7.30 (1 H, d, J = 8.2 Hz), 7.55 (1 H, d, J = 8.2 Hz), 7.56 (1H, s); MS (negative) m/z 390 (M − 1)$^-$; $[\alpha]^{27}_D = -62.1°$ (c = 1.39, 1 M NaOH). Anal. ($C_{16}H_{16}Cl_2FNO_5 \cdot 0.2H_2O \cdot 0.2Py$)[42] C, H, N.

(+)−(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-((*R)-1-(3,4-dichlorophenyl)propoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (+)-11bq:** a white powder; mp >165 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 0.78 (3 H, t, J = 7.2 Hz), 1.50−1.68 (1 H, m), 1.70−1.89 (1 H, m), 2.03−2.37 (4 H, m), 2.38−2.62 (2 H, m), 3.83−3.95 (1 H, m), 4.34 (1 H, t, J = 6.8 Hz), 7.26 (1 H, d, J = 8.2 Hz), 7.51 (1 H, s), 7.55 (1 H, d, J = 8.2 Hz); MS (negative) m/z 404 (M − 1)$^-$; $[\alpha]^{26}_D = +68.4°$ (c = 1.04, 1 M NaOH). Anal. ($C_{17}H_{18}Cl_2FNO_5 \cdot 0.5H_2O \cdot 0.2Py$)[42] C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-((*S)-1-(3,4-dichlorophenyl)propoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11br:** a white powder; mp >170 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 0.81 (3 H, t, J = 7.3 Hz), 1.52−1.70 (1 H, m), 1.70−1.90 (1 H, m), 2.06−2.36 (2 H, m), 2.38−2.62 (2 H, m), 3.70−3.82 (1 H, m), 4.28 (1 H, t, J = 6.7 Hz), 7.30 (1 H, d, J = 8.2 Hz), 7.56 (1 H, s), 7.57 (1 H, d, J = 8.2 Hz); MS (negative) m/z 404 (M − 1)$^-$; $[\alpha]^{29}_D = -71.6°$ (c = 1.21, 1 M NaOH). Anal. ($C_{17}H_{18}Cl_2FNO_5 \cdot 1.2H_2O$) C, H, N.

(+)−(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-((*R)-1-(3,4-dichlorophenyl)butoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (+)-11bs:** a white powder; mp >188 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 0.84 (3 H, t, J = 7.4 Hz), 1.04−1.38 (2 H, m), 1.42−1.64 (1 H, m), 1.70−1.86 (1 H, m) 2.00−2.39 (4 H, m), 3.83−3.98 (1 H, m), 4.42 (1 H, t, J = 6.8 Hz), 7.27 (1 H, d, J = 9.5 Hz), 7.50−7.59 (2 H, m); MS (negative) m/z 418 (M − 1)$^-$; $[\alpha]^{30}_D = +63.9°$ (c = 0.82, 1 M NaOH). Anal. ($C_{18}H_{20}Cl_2FNO_5 \cdot 0.3H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-((*S)-1-(3,4-dichlorophennyl)butoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bt:** a white powder; mp >190 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 0.86 (3 H, t, J = 7.2 Hz), 1.12−1.40 (2 H, m), 1.46−1.64 (1 H, m), 1.70−1.86 (1 H, m), 2.12−2.34 (2 H, m), 2.38−2.64 (2 H, m), 3.68−3.83 (1 H, m), 4.36 (1 H, t, J = 6.6 Hz), 7.30 (1 H, d, J = 8.4 Hz), 7.53−7.60 (2 H, m); MS (negative) m/z 418 (M − 1)$^-$; $[\alpha]^{26}_D = -63.3°$ (c = 1.07, 1 M NaOH). Anal. ($C_{18}H_{20}Cl_2FNO_5 \cdot 2H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(diphenylmethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bu: a white powder; mp >230 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.23−2.53 (4 H, m), 4.01−4.08 (1 H, m), 5.61 (1 H, s), 7.35−7.44 (10 H, m); MS (negative) m/z 384 (M − 1)$^-$; $[\alpha]^{26}_D = -29.8°$ (c = 1.04, 1 M NaOH). Anal. ($C_{21}H_{20}FNO_5 \cdot 1.2H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(bis(4-chlorophenyl)-methoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bv: a white powder; mp >215 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.25−2.49 (4 H, m), 3.98−4.07 (1 H, m), 5.59 (1 H, s), 7.34−7.44 (8 H, m); MS (negative) m/z 452 (M − 1)$^-$; $[\alpha]^{25}_D = -18.4°$ (c = 0.17, 1 M NaOH). Anal. ($C_{21}H_{18}Cl_2FNO_5 \cdot 0.8H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(bis(4-fluorophenyl)-methoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bw: a white powder; mp >190 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.25−2.49 (4 H, m), 3.98−4.07 (1 H, m), 5.59 (1 H, s), 7.34−7.44 (8 H, m); MS (negative) m/z 420 (M − 1)$^-$; $[\alpha]^{24}_D = -24.5°$ (c = 1.05, 1 M NaOH). Anal. ($C_{21}H_{18}F_3NO_5 \cdot 1H_2O \cdot 0.1Py$)[42] C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(bis(3,4-dichlorophenyl)methoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11bx: a white powder; mp >206 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.26−2.47 (4 H, m), 3.96−4.10 (1 H, m), 5.57 (1 H, s), 7.31 (1 H, d, J = 8.2 Hz), 7.53 (1 H, d, J = 8.2 Hz), 7.55 (1 H, s); MS (negative) m/z 520 (M − 1)$^-$; $[\alpha]^{31}_D = -5.1°$ (c = 0.42, 1 M NaOH). Anal. ($C_{21}H_{16}Cl_4FNO_5$) C, H, N.

**(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-((naphthalen-1-yl)-methoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxyl-

ic acid (−)-11by: a white powder; mp >185 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.23−2.48 (4 H, m), 4.15−4.21 (1 H, m), 5.02 (1 H, d, J = 11.9 Hz), 5.09 (1 H, d, J = 11.9 Hz), 7.50−7.68 (4 H, m), 7.94−8.05 (2 H, m), 8.15 (1 H, d, J = 8.1 Hz); MS (negative) m/z 358 (M − 1)$^-$; $[\alpha]^{26}_D = -25.7°$ (c = 0.19, 1 M NaOH). Anal. ($C_{19}H_{18}FNO_5 \cdot 1.5H_2O \cdot 0.05Py$)[42] C, H, N.

(+)−(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-((naphthalen-2-yl)-methoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (+)-11bz: a white powder; mp >210 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.25−2.55 (4 H, m), 4.10−4.19 (1 H, m), 4.73−4.84 (2 H, m), 7.58−7.61 (3 H, m), 7.92−7.99 (4 H, m); MS (negative) m/z 358 (M − 1)$^-$; $[\alpha]^{29}_D = +5.7°$ (c = 0.12, 1 M NaOH) Anal. ($C_{19}H_{18}FNO_5 \cdot 1.2H_2O$) C, H, N.

(+)−(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-((*R)-1-(naphthalen-2-yl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (+)-11ca:** a white powder; mp >185 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 1.47 (3 H, d, J = 6.4 Hz), 2.05 (1 H, dd, J = 7.6, 13.8 Hz), 2.10−2.16 (1 H, m), 2.24−2.38 (2 H, m), 3.96 (1 H, dt, J = 5.0, 7.6 Hz), 4.75−4.80 (1 H, m), 7.51−7.60 (3 H, m), 7.84 (1 H, s), 7.93−7.98 (3 H, m); MS (negative) m/z 372 (M − 1)$^-$; $[\alpha]^{22}_D = +72.4°$ (c = 0.53, 1 M NaOH). Anal. ($C_{20}H_{20}FNO_5 \cdot 0.6H_2O \cdot 0.05Py$)[42] C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-((*S)-1-(naphthalen-2-yl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11cb:** a white powder; mp >188 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 1.49 (3 H, d, J = 6.4 Hz), 2.20 (1 H, dd, J = 2.0, 7.8 Hz), 2.27−2.31 (1 H, m), 2.45−2.62 (2 H, m), 3.81 (1 H, dd, J = 7.5, 12.5 Hz), 4.71−4.80 (1 H, m), 7.55−7.62 (3 H, m), 7.89−8.01 (4H, m); MS (negative) m/z 372 (M − 1)$^-$; $[\alpha]^{22}_D = -36.1°$ (c = 0.49, 1 M NaOH). Anal. ($C_{20}H_{20}FNO_5 \cdot 0.4\ H_2O \cdot 0.1Py$)[42] C, H, N.

(−)-(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-3-(thiophenylmethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-11cc: a white powder; mp >212 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.28−2.51 (4 H, m), 4.09−4.13 (1 H, m), 4.77−4.79 (2 H, m), 7.50 (1 H, dd, J = 7.9, 7.9 Hz), 7.68 (1 H, d, J = 7.9 Hz), 7.73 (1 H, d, J = 7.9 Hz), 7.76 (1 H, s); MS (negative) m/z 314 (M − 1)$^-$; $[\alpha]^{28}_D = -11.6°$ (c = 0.36, 1 M NaOH). Anal. ($C_{13}H_{14}FNO_5S \cdot 0.3H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*S*,5*R*,6*R*)-2-Amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-12c: a white powder; mp >243 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 2.06 (1 H, dd, J = 4.3, 14.8 Hz), 2.18−2.30 (1 H, m), 2.30−2.40 (1 H, m), 2.65−2.83 (1 H, m), 4.48−4.58 (3 H, m), 7.29 (1 H, d, J = 7.9 Hz), 7.54 (1 H, d, J = 7.9 Hz), 7.56 (1H, s); MS (negative) m/z 376 (M − 1)$^-$; $[\alpha]^{27}_D = -28.3°$ (c = 0.33, 1 N NaOH). Anal. ($C_{15}H_{14}Cl_2FNO_5 \cdot 0.2H_2O$) C, H, N.

(−)-(1*R*,2*R*,3*S*,5*R*,6*R*)-2-Amino-3-(bis(4-chlorophenyl)-methoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (−)-12d: a white powder; mp >260 °C (dec); ^{1}H NMR (300 MHz, D_2O, TMSP) δ 1.98−2.12 (1 H, m), 2.14−2.26 (1 H, m), 2.29−2.39 (1 H, m), 2.55−2.72 (1 H, m), 4.46−4.60 (1 H, m), 5.58 (1 H, s), 7.33−7.47 (8 H, m); MS (negative) m/z 452 (M − 1)$^-$; $[\alpha]^{27}_D = -25.3°$ (c = 0.30, 1 M NaOH). Anal. ($C_{21}H_{18}Cl_2FNO_5$) C, H, N.

Pharmacology. Cell Culture. CHO cell lines stably expressing rat mGluR1a, mGluR2, mGluR3, mGluR4, mGluR6, and mGluR7 were cultured in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% dialyzed fetal bovine serum, 2 mM glutamine, 1% proline, 1 mM sodium pyruvate, 1 mM succinic acid, 50 U/mL penicillin, and 50 μg/mL streptomycin. The cells were maintained at 37 °C in the humidified atmosphere of a 5% CO_2 incubator.

[^{3}H]-(1*S*,2*S*,3*S*,5*R*,6*S*)-2-Amino-3-fluorobicyclo[3.1.0]-hexane-2,6-dicarboxylic Acid Binding and [^{3}H]-9 Binding. The binding study using [^{3}H]-(1*S*,2*S*,3*S*,5*R*,6*S*)-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid was described.[12] CHO cells stably expressing mGluRs 2 or 3 were collected by centrifugation at 1000 rpm for 5 min. The cells were homogenized with 50 mM Tris-HCl buffer (pH 7.4), and centrifuged at 48000g for 20 min at 4 °C. The pellet was suspended in 50 mM Tris-HCl buffer (pH 7.4) and incubated at 37 °C for 15 min, after which the pellet was washed twice with 50 mM Tris-HCl buffer (pH 7.4). The pellet obtained was then suspended in 50 mM Tris-HCl buffer (pH 7.4) containing 2 mM $MgCl_2$, and served as a crude membrane preparation. The binding reaction was initiated by incubating 0.5 mL of the crude membrane preparation with [^{3}H]-(1*S*,2*S*,3*S*,5*R*,6*S*)-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (3 nM). The reaction mixture was incubated for 1 h at 25 °C. [^{3}H]-**9** binding to mGluR 7 was performed according to the method of Wright et al.[36] CHO cells expressing mGluR 7 were pelleted and homogenized with 10 mM potassium phosphate buffer containing 100 mM potassium bromide (pH 7.6), and the membrane preparation was incubated with [^{3}H]-**9** (10 nM) on ice for 45 min. The reaction was terminated by rapid filtration through Whatman GF/C glass fiber filters presoaked with 0.3% polyethyleneimine, after which the filters were washed three times with 3 mL of ice-cold 50 mM HEPES buffer (pH 7.4) (for [^{3}H]-(1*S*,2*S*,3*S*,5*R*,6*S*)-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid binding) or 10 mM potassium phosphate buffer containing 100 mM potassium bromide (pH 7.6) (for [^{3}H]-**9** binding), using a multicell harvester M-48R (Brandel Biomedical Research and Development Laboratories, Inc., Gaithersburg, MD). Aquazol-2 scintillator (PerkinElmer Life Sciences, Boston, MA) was added, and the filter-bound radioactivity was measured in a liquid scintillation spectrometer (LS6000TA, Beckman Instruments Inc., Fullerton, CA). Nonspecific binding was determined in the presence of 10 μM **9** for [^{3}H]-(1*S*,2*S*,3*S*,5*R*,6*S*)-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid binding and 10 μM **9** for [^{3}H]-**9** binding.

The concentration of the test compound that caused 50% inhibition of specific bindings of [^{3}H]-(1*S*,2*S*,3*S*,5*R*,6*S*)-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (IC_{50} value) and [^{3}H]-**9** were determined from each concentration−response curve. K_i values for each test compound were calculated using the K_d value obtained from Scatchard analysis.

Measurements of cAMP Formation. Agonist activities for mGluRs 2, 3, 4, and 6 were evaluated by measuring the agonist-dependent inhibition of forskolin-induced cAMP formation in mGluR 2, 3, 4, or 6-expressing CHO cells, as previously described.[12] CHO cells expressing mGluRs 2, 3, 4, 6, or 7 were seeded in 96-well plates at a density of 1.26×10^4 cells per well and grown for 2 days. The media were replaced with fresh medium without 2 mM glutamine, and the cells were then incubated for 4 to 5 h. These cells were preincubated with phosphate-buffered saline (PBS) containing 1 mM 3-isobutyl-1-methylxanthine (IBMX) (PBS−IBMX) for 20 min at 37 °C. The reaction was started by replacing the medium with fresh PBS−IBMX containing 10 μM forskolin and various concentrations of the compound. After incubation for 15 min (mGlu 2, mGlu 3, and mGlu 4) or 30 min (mGlu 6) at 37 °C, the reaction was terminated by adding ice-cold 100% ethanol to yield a concentration of 60% of ethanol, and then settled on ice for 40 min. The supernatants were evaporated and cAMP levels were determined using a cAMP enzyme immunoassay (EIA) system. Antagonist activities of the compound were measured with 3 μM (for mGlu 3), 30 μM (for mGlu 2 and 4), or 40 μM (for mGlu 6) glutamic acid, and the compound was added to the cells 20 min prior to glutamic acid.

Measurements of IP_3 Formation. Agonist activities for mGluRs 1a and 5 were evaluated by measuring IP_3 formation in mGluR 1a or 5 expressing CHO cells. The CHO cells expressing mGluR 1a or 5 were seeded in a 6-well plate at a density of 3.72×10^5 cells per well and grown for 2 days. Media were changed to fresh medium without 2 mM glutamine, and the cells were incubated for 4 to 5 h. The cells were preincubated with incubation buffer (pH 7.4, 20 mM HEPES, 150 mM NaCl, 1.5 mM KCl, 1.8 mM $CaCl_2$, 0.8 mM $MgSO_4$, 25 mM glucose, and 10 mM LiCl) for 20 min at 37 °C. The reaction was started by replacing the medium with fresh incubation buffer containing various concentrations of the compounds. After incubation for 15 s at room temperature, the reaction was terminated with ice-cold 20% perchloric acid (final concentration: 4%), and then left to settle on ice for 20 min. The cells were scraped off, and cell suspensions were centrifuged at 15000 rpm for 10 min. The supernatants were neutralized

to pH 7.5 by titrating with ice-cold 1.5 M KOH containing 60 mM HEPES, and recentrifuged to remove any $KClO_4$ precipitate. The resulting supernatants were evaporated and the content of IP_3 was quantitatively determined using the D-*myo*-inositol 1,4,5-triphoshate (IP_3) [^{3}H] assay system. Antagonist activities of the compounds were measured with 30 μM glutamic acid.

Pharmacokinetics. Animals. Male Wistar rats (Charles River, Japan) were used in the experiment at 7 weeks of age. All animals in these experiments were used after acclimation for at least one week. The rats were allowed water and standard laboratory diet (MF, Oriental Yeast Co., Japan) ad libitum during acclimation. Environmental conditions were controlled during breeding: relative humidity 50 ± 20%, temperature 23 ± 3 °C. The animals were fasted overnight (about 18 h) before and for 4 h after dosing. Drinking water was freely available at all times.

Plasma Concentrations. After administration of compounds (−)-**11al**, (−)-**11ay**, (−)-**11be**, (−)-**11bu**, and (+)-**11bz**, 0.3 mL blood samples were taken from the right jugular vein using heparinized syringes. Each blood sample was taken into a tube, and the plasma was separated by centrifugation (2056 × g, 4 °C, 10 min). To a 50 μL aliquot of plasma sample was added 200 μL of methanolic IS working solution (250 ng/mL), and the tube was vortexed and centrifuged at 2056*g* (4 °C) for 10 min. The methanolic supernatant was filtered through a centrifugal filter unit (0.22 μm), and a 5 μL aliquot of the sample was injected onto the LC/ESI-MA/MA system. LLOQ of plasma was 1 ng/mL.

Brain Concentrations. After administration of compounds (−)-**11al**, (−)-**11ay**, (−)-**11be**, (−)-**11bu**, and (+)-**11bz**, blood samples were taken from the right jugular vein using heparinized syringes and the plasma was separated by centrifugation (2056*g*, 4 °C, 10 min). Rats were decapitated at a designated time. The brain (cerebrum) was immediately excised and weighed, and 4-fold saline was added followed by homogenization. To a 50 μL aliquot of plasma sample was added 200 μL of methanolic internal standard working solution (250 ng/mL), and the tube was vortexed and centrifuged at 2056*g* (4 °C) for 10 min. The methanolic supernatant was filtered through a centrifugal filter unit (0.22 μm), and a 5 μL aliquot of the sample was injected onto the LC/ESI-MA/MA system. To a 100 μL aliquot of brain homogenate sample was added 400 μL of methanolic internal standard working solution (2.5 g/mL), and the tube was vortexed and centrifuged at 2056*g* (4 °C) for 10 min. The methanolic supernatant was evaporated to dryness with nitrogen at 40 °C. The residue was reconstituted in 100 μL of methanol. The reconstituted sample was injected onto the LC/ESI-MA/MA system. LLOQs of plasma and brain were 1 ng/mL and 1.5 ng/g, respectively.

Acknowledgment. The authors thank Professor Sigetada Nakanishi at Department of Biological Sciences, Kyoto University Faculty of Medicine, for provision of CHO cell lines stably expressing rat mGluRs 1a, 2, 3, 4, 6, and 7.

Supporting Information Available: Table of elemental analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Colinridge, G. L.; Lester, R. A. Excitatory amino acid receptors in the vertebrate central nervous system. *Pharmacol. Rev.* **1989**, *40*, 143−210.
(2) Monaghan, D. T.; Bridges, R. J.; Cotman, C. W. The excitatory acid receptors: their classes, pharmacology, and distinct properties in the function of the central nervous system. *Annu. Rev. Pharmacol. Toxicol.* **1989**, *29*, 365−402.
(3) Nakanishi, S. Molecular diversity of glutamate receptors and implications for brain function. *Science* **1992**, *258*, 597−603.
(4) Pin, J. P.; Duvoisin, R. The metabotropic glutamate receptors: structure and functions. *J. Neurochem.* **1992**, *58*, 1184−1186.
(5) Schoepp, D. D.; Conn, P. J. Metabotropic glutamate receptors in brain function and pathology. *Trends Pharmacol. Sci.* **1993**, *14*, 13−20.
(6) Bockaert, J.; Pin, J.; Fagni, L. Metabotropic glutamate receptors: an original family of G protein-coupled receptors. *Fundam. Clin. Pharmacol.* **1993**, *7*, 473−485.
(7) Nakanishi, S.; Masu, M. Molecular diversity and functions of glutamate receptors. *Annu. Rev. Biophys. Biomol. Struct.* **1994**, *23*, 319−348.
(8) Hollmann, M.; Heinemann, S. Cloned glutamate receptors. *Annu. Rev. Neurosci.* **1994**, *17*, 31−108
(9) Conn, P. J.; Pin, J.-P. Pharmacology and functions of metabotropic glutamate receptors. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 205−237.
(10) Schoepp, D. D.; Johnson, B. G.; Monn, J. A. Inhibition of cyclic AMP formation by a selective metabotropic glutamate receptor agonist. *J. Neurochem.* **1992**, *58*, 1184−1186.
(11) Nakajima, Y.; Iwakabe, H.; Akazawa, C.; Nawa, H.; Shigemoto, R.; Mizuno, N.; Nakanishi, S. Molecular characterization of a novel retinal metabotropic glutamate receptor mGluR6 with a high agonist selectivity for L-2-amino-4-phosphonobutyrate. *J. Biol. Chem.* **1993**, *268*, 11868−11873.
(12) Meldrum, B. S. Glutamate as a neurotransmitter in the brain: review of physiology and pathology. *J. Nutr.* **2000**, *130*, 1007S−1015S.
(13) Nakazato, A.; Kumagai, T.; Sakagami, K.; Yoshikawa, R.; Suzuki, Y.; Chaki, S.; Ito, H.; Taguchi, T.; Nakanishi, S.; Okuyama, S. Synthesis, SARs, and pharmacological characterization of 2-amino-3 or 6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as potent, selective, and orally active group II metabotropic glutamate receptor agonists. *J. Med. Chem.* **2000**, *43*, 4893−4909.
(14) Cartmell, J.; Monn, J. A.; Schoepp, D. D. Attenuation of specific PCP-evoked behaviors by the potent mGluR2/3 receptor agonist, LY379268 and comparison with the atypical antipsychotic, clozapine. *Psychopharmacology* **2000**, *148*, 423−429.
(15) Moghaddam, B.; Adams, B. W. Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. *Science* **1998**, *281*, 1349−1352.
(16) Grillon, C.; Cordova, J.; Levine, L. R.; Morgan, C. A., 3rd. Anxiolytic effects of a novel group II metabotropic glutamate receptor agonist (LY354740) in the fear-potentiated startle paradigm in humans. *Psychopharmacology* **2003**, *168*, 446−454.
(17) Tizzano, J. P.; Griffey, K.; Schoepp, D. D. The anxiolytic action of mGlu2/3 receptor agonist, LY354740, in the fear-potentiated startle model in rats in mechanistically distinct from diazepam. *Pharmacol., Biochem. Behav.* **2002**, *73*, 367−374.
(18) Helton, D. R.; Tizzano, J. P.; Monn, J. A.; Schoep, D. D.; Kallman, M. J. Anxiolytic and side-effect profile of LY354740: a potent, highly selective, orally active agonist for group II metabotropic glutamate receptors. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 651−660.
(19) Monn, J. A.; Valli, M. J.; Massey, S. M.; Wright, R. A.; Salhoff, C. R.; Johnson, B. G.; Howe, T.; Alt, C. A.; Rhodes, G. A.; Robey, R. L.; Griffey, K. R.; Tizzano, J. P.; Kallman, M. J.; Helton, D. A.; Schoepp, D. D. Design, synthesis, and pharmacological characterization of (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740): a potent, selective, and orally active group 2 metabotropic glutamate receptor agonist possessing anticonvulsant and anxiolytic properties. *J. Med. Chem.* **1997**, *40*, 528−537.
(20) Levine, L.; Gaydos, B.; Sheehan, D.; Goddard, A. W.; Feighner, J.; Potter, W. Z.; Schopp, D. D. The mGlu2/3 receptor agonist, LY354740, reduces panic anxiety induced by a CO_2 challenge in patients diagnosed with panic disorder. *Neuropharmacology* **2002**, *43*, 294.
(21) Ornstein, P. L.; Bleisch, T. J.; Arnold, M. B.; Wright, R. A.; Johnson, B. G.; Schoepp, D. D. 2-Substituted (2*SR*)-2-amino-2-((1*SR*,2*SR*)-2-carboxycycloprop-1-yl)glycines as potent and selective antagonists of group II metabotropic glutamate receptors. 1. Effects of alkyl, arylalkyl, and diarylalkyl substitution. *J. Med. Chem.* **1998**, *41*, 346−357.
(22) Ornstein, P. L.; Bleisch, T. J.; Arnold, M. B.; Kennedy, J. H.; Wright, R. A.; Johnson, B. G.; Tizzano, J. P.; Helton, D. R.; Kallman, M. J.; Schoepp, D. D. 2-Substituted (2*SR*)-2-amino-2-((1*SR*,2*SR*)-2-carboxycycloprop-1-yl)glycines as potent and selective antagonists of group II metabotropic glutamate receptors. 2. Effects of aromatic substitution, pharmacological characterization, and bioavailability. *J. Med. Chem.* **1998**, *41*, 358−378.
(23) Chaki, S.; Yoshikawa, R.; Hirota, S.; Shimazaki, T.; Maeda, M.; Kawashima, N.; Yoshimizu, T.; Yasuhara, A.; Sakagami, K.; Okuyama, S.; Nakanishi, S.; Nakazato, A. MGS0039: a potent and selective group II metabotropic glutamate receptor antagonist with antidepressant-like activity. *Neuropharmacol.*, in press.
(24) Jane, D. E.; Jones, P. L. St. J.; Pook, P. C.-K.; Tse, H.-W.; Watkins, J. C. Actions of two new antagonists showing selectivity for different subtypes of metabotropic glutamate receptor in the neonatal rat spinal cord. *Br. J. Pharmacol.* **1994**, *112*, 809−816.
(25) Pelliciari, R.; Marinozzi, M.; Natalini, B.; Costantino, G.; Luneia, R.; Giorgi, G.; Moroni, F.; Thomsen C. Synthesis and pharmacological characterization of all sixteen stereoisomers of 2-(2′-

carboxy-3′-phenylcyclopropyl)glycine. Focus on (2*S*,1′*S*,2′*S*,3′*S*)-2-(2′-carboxy-3′-phenylcyclopropyl)glycine, a novel and selective group II metabotropic glutamate receptor antagonist. *J. Med. Chem.* **1996**, *39*, 2259−2269.
(26) Kew, J. N. C.; Ducarre, J.-M.; Woltering, T.; Adam, G.; Mutel, V.; Kemp, J. A. Frequency-dependent presynaptic autoinhibition by group II metabotropic glutamate receptors at the medial perforant path input to the dentate gyrus. *29th Annu. Meet. Soc. Neurosci. (Oct. 23−28, Miami)* **1999**, Abstr. 494.10.
(27) Shao, H.; Goodman, M. An enantionmeric synthesis of *allo*-threonines and *β*-hydroxyvalines. *J. Org. Chem.* **1996**, *61*, 2582−2583.
(28) Review: Lohray, B. B. Cyclic sulfites and cyclic sulfates: Epoxide like synthons. *Synthesis* **1992**, 1035−1052.
(29) Gao, Y.; Sharpless, K. B. Vicinal diol cyclic sulfates: Like epoxides only more reactive. *J. Am. Chem. Soc.* **1988**, *110*, 7538−7539.
(30) Wessel, H.-P.; Iversen, T.; Bundle, D. R. Acid-catalysed benzylation and allylation by alkyl trichloroacetimidates. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247−2250.
(31) Widmer, U. A convenient benzylation procedure for *β*-hydoxy esters. *Synthesis* **1987**, 568−570.
(32) Vaultier, M.; Knouzi, N.; Carrié, R. Reaction D'azines en amines primaries par une methode generale utilisant la reaction de Staudinger. *Tetrahedron Lett.* **1983**, *24*, 763−764.
(33) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. Sixty years of Staudinger reaction. *Tetrahedron* **1981**, *37*, 437−472.
(34) Radüchel, B. Inversion of configuration of secondary alcohols, in particular in the steroid and prostaglandin series. *Synthesis* **1980**, 292−295.
(35) Jauch, J. A short synthesis of Mniopetal F. *Eur. J. Org. Chem.* **2001**, 473−476.
(36) Wright, R. A.; Arnold, M. B.; Wheeler, W. J.; Ornstein, P. L.; Schoepp, D. D. Binding of [^{3}H](2S,1′S,2′S)-2-(9-xanthylmethyl)-2-(2′-carboxycyclopropyl)glycine ([^{3}H]LY341495) to cell membranes expressing recombinant human group III metabotropic glutamate receptor subtypes. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2000**, *362*, 546−554.
(37) Tanabe, Y.; Masu, M.; Ishii, T.; Shigemoto, R.; Nakanishi, S. A family of metabotropic glutamate receptors. *Neuron* **1992**, *8*, 169−179.
(38) Seishima, M.; Yada, Y.; Nagao, S.; Mori, S.; Nozawa, Y. Defective formation of inositol 1,4,5-trisphosphate in bradykinin-stimulated fibroblasts from progressive systemic sclerotic patients. *Biochem. Biophys. Res. Commun.* **1988**, *156*, 1077−1082.
(39) Fu, T.; Okano, Y.; Nozawa, Y. Bradykinin-induced generation of inositol 1,4,5-trisphosphate in fibroblasts and neuroblastoma cells: effects of pertussis toxin, extracellular calcium, and down-regulation of protein kinase C. *Biochem. Biophys. Res. Commun.* **1988**, *157*, 1077−1082.
(40) Kawabata, S.; Tsutsumi, R.; Kohara, A.; Yamaguchi, T.; Nakanishi, S.; Okada, M. Control of calcium oscillations by phosporylation of metabotropic glutamate receptors. *Nature* **1996**, *383*, 89−92.
(41) Aramori, I.; Nakanishi, S. Signal transduction and pharmacological characteristics of a metabotropic glutamate receptor, mGluR1, in transfected CHO cells. *Neuron* **1992**, *8*, 757−765.
(42) Py: Pyridine. The existence of pyridine in the crystal was supported by ^{1}H NMR spectra. For example, ^{1}H NMR spectral data of **11ad** supported the existence of pyridine (^{1}H NMR (300 MHz, D_2O, TMSP) δ 7.71−7.83 (m, 2 H) 8.24 (t, J = 8.1 Hz, 1 H) 8.59−8.71 (m, 2 H)).

JM0400294