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Stereoselective Reduction of Cyclopropylalkaones Possessing a Difluoromethylenephosphonate Group at the Ring: Application to Stereoselective Synthesis of Novel Cyclopropane Nucleotide Analogues

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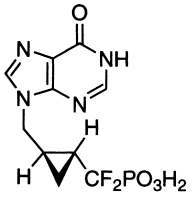
Abstract—Difluoro{(1*S**,2*S**)-2-[(1*S**)-1-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethyl]cyclopropyl}methylphosphonic acid **12a** and the related analogues were prepared as 'multi-substrate analogue' inhibitors for purine nucleoside phosphorylase. Reduction of diethyl [(1*S**,2*S**)-2-acethylcyclopropyl](difluoro)methylphosphonate **8a** with K-Selectride at a low temperature proceeded from the less-hindered face of the carbonyl in the bisected *s-cis* conformation to give the corresponding cyclopropylalkanol **9a** in high diastereoselectivity (94% de). In an analogous manner, several cyclopropylalkanols **8b**–**g** possessing a difluoromethylene phosphonate functional group at the ring were stereoselectively synthesized. The cyclopropylalkanol **9a** was manipulated to the nucleotide analogue **12a** through a conventional method. The diastereomeric nucleotide analogue **15** was prepared from **9a** via the Mitsunobu inversion. Preliminary results on an assay of PNP inhibitory activity of **9a** and **15** are presented.

Introduction

Purine nucleoside phosphorylase (PNP: EC. 2.4.2.1) is a ubiquitous enzyme of the purine salvage pathway. It catalyzes the reversible phosphorylation of ribo- and 2′-deoxyribo-nucleosides of guanine and hypoxanthine in higher organisms, as well as of adenine in some prokaryotes.[1] A large part of interest in PNP focuses on its potential as a drug target. Inhibitors of PNP have been suggested to have therapeutic value in the treatment of T-cell proliferative disease such as T-cell leukemia.[2–4]

Since PNP accomplishes the reversible phosphorylation of the purine nucleosides via a ternary complex of enzyme, nucleoside, and orthophosphate, compounds that contain covalently linked elements of both substrates (nucleoside and orthophosphate) in their structure are expected to act as a 'multi-substrate analogue' inhibitor for PNP.[5a] Therefore, a number of metabolically stable acyclic nucleotide analogues containing a purine and a phosphate-like moiety have been synthesized.[5]

During our studies on the design and synthesis of multi-substrate analogue PNP-inhibitors based on α,α-difluoromethylenephosphonate as a mimetic of orthopthosphate,[6] we found a novel cyclopropane nucleotide analogue **1** to have a significant binding affinity (Ki=5.4 nM) to the PNP purified from *Cellulomonas* sp.[6b] As a part of our program to examine the structure–activity relationship as well as the inhibitory mechanism of this class of inhibitors, it was necessary to synthesize a wide variety of the cyclopropane nucleotide analogues as exemplified by the general structure **2**. In these nucleotide analogues, free rotation of the single bonds from the nucleobase to the cyclopropanes would be partially restricted due to steric repulsion between the adjacent substituents on the cyclopropane. Therefore, such modification brings **1** to conformationally more rigid nucleotide analogues that may become useful tools for examining the active conformation of the nucleobase in **1** toward the PNP. Herein, we describe a method for stereoselective introduction of alkyl groups (R) to the side-chain. We also report inhibitory potencies of some of the synthesized compounds toward *Cellulomonas* sp. PNP.



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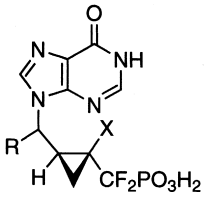

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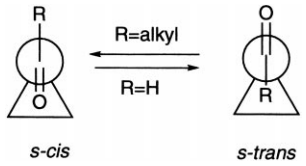
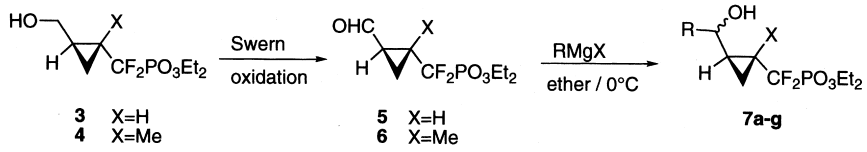


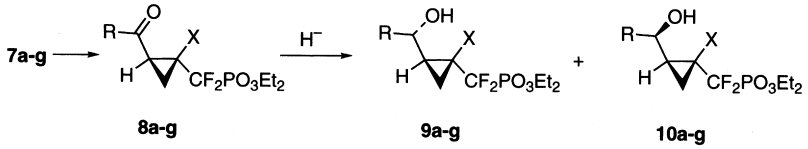
Figure 1.

on *s-trans*- or *s-cis*-bisected conformer for introducing a hydroxyl functionality stereoselectively to the side chain of cyclopropanes.[8]

Keeping this in mind for the stereoselective synthesis of the key intermediates of **2**, we first examined the alkylation of the cyclopropyl aldehydes **5** and **6**, prepared by Swern oxidation of the alcohols **3**[9] and **4**,[9] with



Scheme 1. a: X=H, R=Me; **b**: X=Me, R=Me; **c**: X=H, R=Ph; **d**: X=Me, R=Ph; **e**: X=H, R=$PhCH_2$; **f**: X=H, R=*c*-$C_6H_{11}CH_2$; **g**: X=H, R=2-propenyl.



Scheme 2. a: X=H, R=Me; **b**: X=Me, R=Me; **c**: X=H, R=Ph; **d**: X=Me, R=Ph; **e**: X=H, R=$PhCH_2$; **f**: X=H, R=*c*-$C_6H_{11}CH_2$; **g**: X=H, R=2-propenyl.

Table 1. Reduction of **8a**–**g** with hydride reagents

Entry	Substrate	Reagent/conditions	Time (min)	Yield (%)	**9**:**10**[a]
1	**8a**	$NaBH_4$/MeOH/20°C	15	97	71:29[b]
2	**8a**	*n*-Bu_4NBH_4/MeOH/0°C	10	99	76:24[b]
3	**8a**	9-BBN/THF/0°C	180	64	67:33
4	**8a**	$KB(C_6H_5)_3H$/THF/−78°C	30	55	91:9
5	**8a**	L-Selectride/THF/−78°C	5	49	96:4
6	**8a**	K-Selectride/THF/−78°C	20	77	97:3
7	**8b**	K-Selectride/THF/−78°C	30	57	99:1
8	**8c**	K-Selectride/THF/ −78°C	30	65	99:1
9	**8d**	K-Selectride/THF/ −78°C	30	82	99:1
10	**8e**	K-Selectride/THF/ −78°C	30	51	99:1
11	**8f**	K-Selectride/THF/ −78°C	30	49	99:1
12	**8g**	K-Selectride/THF/ −78°C	30	63	99:1
13	**8a**	DIBAL-H/THF/ −78°C	60	12	3:97

[a] The ratios were determined by ^{31}P NMR ($CDCl_3$) analysis of the crude materials.
[b] The diastereoselectivity was not improved when the reaction was carried out at −78°C.

Result and Discussion

Stereoselective synthesis of cyclopropylalkanols 9 and 10

It has been recognized that cyclopropyl aldehydes and cyclopropyl ketones preferentially exist in bisected conformations (*s-trans* and *s-cis* conformers) due to the characteristic stereoelectronic effects of the cyclopropane ring[7] (Fig. 1). The *s-trans* conformer is believed to be predominant in cyclopropyl aldehydes, while the *s-cis* conformer is predominant in cyclopropyl ketones. Recently, alkylation of cyclopropyl aldehydes with Grignard reagents as well as the reduction of cyclopropyl ketones with metal hydride reagents have been proved to proceed through either

various Grignard reagents (MeMgCl, PhMgBr, $PhCH_2MgCl$, *c*-$C_6H_{11}CH_2MgBr$, and $CH_2{=}CHCH_2MgBr$) at 0°C in ether (Scheme 1). While all reactions gave the desired adducts **7a**–**g**, no diastereoselectivity was observed for these reactions.[†] The results might be attributed to the less steric impedance of the substituents (X) on the

[†] The diastereomeric mixtures **7a**–**g** were not readily separated by column chromatography on silica gel except for **7c**. Although **7a** (1:1) was transformed directly to a mixture of **11a** and **14** under the Mitsunobu coupling, isolations of diastereomerically pure **11a** and **14** from the crude preparation failed of success: it largely depends upon the similar polarities of the two diastereomers. Therefore it was necessary to develop a facile method for the highly stereoselective synthesis of **9** and **10**.

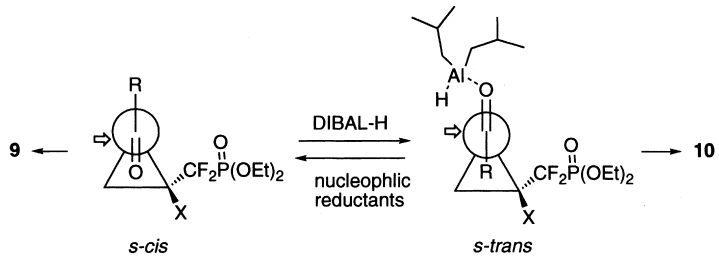


Figure 2.

cyclopropane ring in the *s-trans*-bisected conformer of the cyclopropyl aldehydes **5** and **6**.

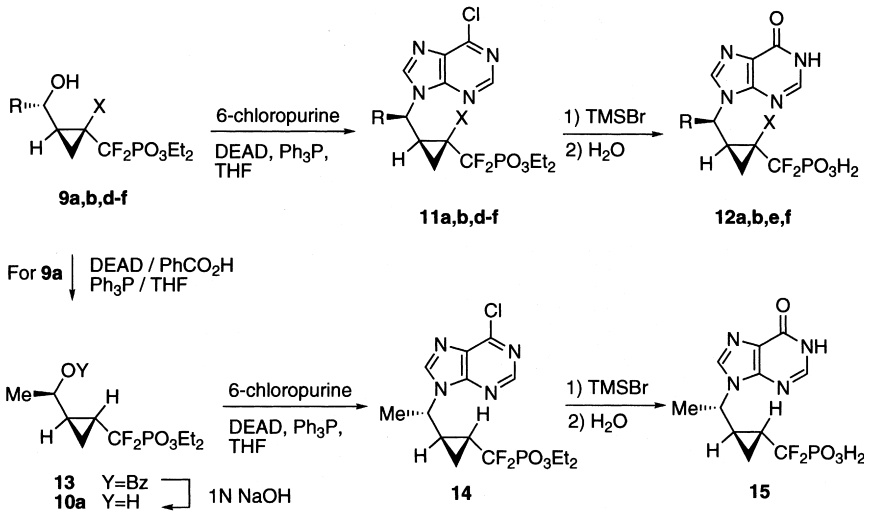
To obtain the diastereomerically pure alcohols for **7a**–**g**, we next examined metal hydride reduction of the ketones **8a**–**g**, which were obtained by oxidation of diastereomixtures of **7a**–**g** with Jones reagent (Scheme 2 and Table 1).

The stereoselective reduction of **8a** was examined using various reductants. As seen in Table 1, when sodium borohydride ($NaBH_4$), tetrabutylammonium borohydride (n-Bu_4NBH_4), or 9-borabicyclo[3.3.1]nonane (9-BBN) was used as a reductant, low diastereoselectivity (34–52 de) in favor of the diastereomer **9a** with high yields was obtained (entries 1–3). The diastereoselectivity markedly increased to 82 and 92% de when the reduction was carried out with either potassium triphenylborohydride ($KB(C_6H_5)_3H$) or lithium tri-*sec*-butylborohydride (L-Selectride) in THF at −78°C (entries 4 and 5). However, the yield for these reactions was modest owing to partial decomposition of the reduction products under the conditions. The undesired side-reactions were suppressed by replacement of the reductants with potassium tri-*sec*-butylborohydride (K-Selectride). Under the conditions (−78°C in THF), the reduction of ketone **8a** proceeded with good diastereoselectivity (94% de) to give the diastereomer **9a** in 77% yield (entry 6). Using the K-Selerctride reduction, ketones **8b**–**g** were also transformed to the alcohols **9b**–**g** in a highly diastereoselective manner (>98% de) in moderate to good yield (entries 7–12). The results indicated that K-Selectride is an effective reductant generally applicable to stereoselective reduction of this class of cyclopropyl ketones. It was verified that the reduction of **8a** with diisobutylaluminum hydride (DIBAL-H) proceeded with the opposite sense of stereochemistry in good diastereoselectivity (94% de) to give **10a** (entry 13). However, the yield of **10a** was very low; and a substantial amount of the starting materials was recovered.

The stereochemistry of **9a**–**g** and **10a** was first estimated by assuming the reduction to proceed via the Shuto model for the hydride reduction of cyclopropyl ketones,[8] and eventually this was confirmed at the stage of the 6-chloropurine derivative (vide infra). The stereochemical outcome of the reduction with nucleophilic reductants such as L- and K-Selectride might be rationalized by postulating that the hydride was delivered from the sterically less-hindered face of the carbonyl in the *s-cis*-bisected conformer to give **9a**–**g** (Fig. 2). The opposite diastereoselection for the reduction with DIBAL-H might be explained by the relatively electrophilic character of the reductant; coordination of DIBAL-H to the carbonyl alters the preferred conformation to the *s-trans*-bisected conformer. As a result, hydride delivery to the carbonyl from the less-hindered face gave the diastereomer **10a** (Fig. 2). Similar diastereoinversion depending on the nature of reductants was also observed by Shuto et al., in the synthesis of milnacipran analogues.[8]

Transformation of cyclopropylalkanols to nucleotide analogues

Conversion of the alcohols **9** to the target nucleotide



Scheme 3. a: X=H, R=Me; **b**: X=Me, R=Me; **d**: X=Me, R=Ph; **e**: X=H, R=$PhCH_2$; **f**: X=H, R=c-$C_6H_{11}CH_2$.

analogues **12** was accomplished as shown in Scheme 3. Condensation of **9a** with 6-chloropurine under the Mitsunobu conditions [DEAD, Ph_3P, THF] gave 6-chloropurine derivative **11a** in 43% yield, along with the corresponding *N*-7 isomer (20%). The compound **11a** was assigned to be the desired *N*-9 isomer on the basis of ^1H NMR data of the aromatic protons. The C2-H and C8-H of **11a** resonated at δ 8.72 and 8.26 ppm, respectively, while the corresponding signals of the *N*-7 isomer were observed at δ 8.90 and 8.55 ppm. The observed high-field chemical shift of C2-H and C8-H of **11a** suggests that the major isomer should be the *N*-9 isomer.[10] Under the same conditions, alcohols **9b**, **9d**, **9e** and **9f** were transformed to 6-chloropurine derivatives **11b**, **11d**, **11e**, and **11f**, respectively, albeit the yield was modest (9–32%).

The 6-chloropurine derivative **11d** was obtained as single-crystals suitable for X-ray crystallographic analysis. The analysis unambiguously confirmed the relative stereochemistry of **11d** (Fig. 3). At this stage, the K-Selectride reduction of cyclopropyl ketone **8d** was ascertained to proceed to give **9d** in the expected manner.[8] The stereochemistry of alcohols **9a**–**c** and **9e**–**g** was assigned on the basis of their similarity to **9d** in the ^{31}P chemical shifts.‡

Removal of the ethyl protecting group and hydrolysis of a 6-chloropurine for **11a**,**b** and **11e**,**f** were performed by treatment with bromotrimethylsilane (TMSBr) in CH_2Cl_2, followed by hydrolysis with H_2O in one-pot, to give nucleotide analogues **12a**,**b** and **12e**,**f** as amorphous powders.§ The diastereomeric nucleotide analogue **15** was also prepared from **10a** via **14** in a similar manner to that for preparation of **12a**. For this transformation, sufficient amounts of alcohol **10a** were alternatively obtained by the Mitsunobu inversion of **9a** with benzoic acid, followed by hydrolysis.

Finally, inhibition potencies of nucleotide analogues **12a** and **15** were evaluated in comparison with the previously synthesized nucleotide analogue **1**. The preliminary results showed that **12a** and **15** had IC_{50} values of 70 and 90 nM, respectively, for PNP (*Cellulomonas* sp.)-catalyzed phosphorylation of inosine in the presence of 100 mM orthophosphate.[6b,c] Dixon plot analysis revealed that Ki values of **12a** and **15** were 19.6 and 20.4 nM, respectively, and that the binding affinities of the two diastereomers for the PNP derived from *Cellulomonas* sp. were almost the same. Under the same conditions, the IC_{50} and Ki values of **1** have been determined to be 190 and 5.4 nM, respectively.[6b]

The results imply that introduction of a methyl substituent to the side-chain of **1** increases its inhibitory potency for the catalytic reaction of PNP, while the binding affinity for the enzyme protein itself is decreased. Moreover, the observed similarity of **12a** and **15** in binding affinity for the enzyme suggests that the introduced methyl group might not sufficiently work to fix the conformation of the nucleobase interacting with the purine-binding site of the PNP in a desired manner.[5] A clear understanding of how the substitution affects the conformational changes in the nucleobase and the resulting inhibitory activity must await further investigation.

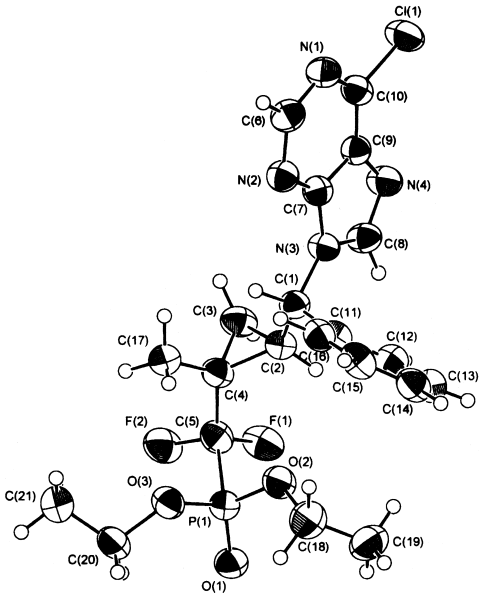


Figure 3. ORTEP drawing of **11d**.

Experimental

All reactions were carried out under nitrogen atmosphere. NMR data were obtained on a Bruker DPX 400 using $CDCl_3$, CD_3OD, or D_2O as a solvent unless otherwise specified. ^{13}C NMR (100 MHz) and ^{31}P NMR (162 MHz) were taken with broad-band ^1H decoupling. The chemical shift data for each signal on ^1H NMR (400 MHz) are expressed as relative ppm from $CHCl_3$ (δ 7.26 ppm) or CH_3OH (δ 3.30 ppm). The chemical shifts of ^{13}C are reported relative to $CDCl_3$ (δ 77.0 ppm) or CD_3OD (δ 49.0 ppm). 3-(Trimethylsily)-d_4-propionic acid, sodium salt (TSP, 0 ppm) was used as external standard for D_2O solution. The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4. ^{19}F NMR spectra (376 MHz) were measured using benzotrifluoride (BTF) as an internal reference. IR spectra were recorded on a JASCO FTIR-620 spectrometer. Mass spectra were measured on a Finnigan TSQ-700 or a VG Auto Spec E spectrometer.

Diethyl difluoro[(1S*,2S*)-2-formylcyclopropyl]methylphosphonate 5. To a stirred solution of oxaryl chloride (1.63 mL, 18.9 mmol) in CH_2Cl_2 (125 mL) was slowly added DMSO (2.68 mL, 37.8 mmol) at −78°C. The mixture was stirred for 30 min at the same temperature. A solution of **3**[9] (4.1 g, 15.8 mmol) in CH_2Cl_2 (30 mL) was added dropwise. The mixture was stirred for 30 min, and then Et_3N (4.75 mL, 78.8 mmol) was added. After being stirred at 0°C for 20 min and at 25°C for 30 min, the mixture was portioned to ether and sat. NH_4Cl. The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give aldehyde **5** (3.8 g, 98%) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 9.40 (1H, d, J=3.9 Hz), 4.33–4.24 (4H, m), 2.73–2.30 (1H, m), 2.25–2.12 (1H, m), 1.46–1.37 (2H, m), 1.46 (6H, t, J=7.2 Hz), IR (neat) 1799,

‡ The phosphorus atom of **9a**–**g** resonated at lower field than that of **10a**–**g** by a factor of 0.4–1.23 ppm (see Experimental section).

§ Hydrolysis of **11d** to the corresponding nucleotide analogue failed: the cyclopropane ring decomposed rapidly under the conditions.

1270 cm^{-1} , EIMS *m/z* 257 (MH^+). This crude aldehyde was used in the next step without any further purification.

Diethyl difluoro[(1*S,2*S**)-2-formyl-1-methylcyclopropyl]-methylphosaphonate 6.** The alcohol **4**[9] (2.7 g, 10 mmol) was oxidized in an analogous manner to that for preparation of **5** to give **6** (2.5 g, 95%) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 9.60 (1H, d, J=3.8 Hz), 4.32–4.22 (4H, m), 2.41–2.35 (1H, m), 1.53–1.48 (1H, m), 1.43 (3H, s), 1.41–1.39 (1H, m), 1.38 (3H, t, J=7.1 Hz), 1.37 (3H, t, J=7.1 Hz); IR (neat) 1710, 1269 cm^{-1}; EIMS *m/z* 270 (M^+). This crude aldehyde was used in the next step without any further purification.

Diethyl [(1*S,2*S**)-2-acethylcyclopropyl](difluoro)methylphosphonate 8a.** To a stirred solution of MeMgCl (7.57 mL of 3.0 M solution in THF; 22.7 mmol) in ether (60 mL) was added aldehyde **5** (4.85 g, 18.9 mmol) in ether (30 mL) under ice-cooling. The mixture was stirred at 0°C for 30 min and at 25°C for 1 h. The reaction was quenched with saturated NH_4Cl. The resulting mixture was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a diastereomeric mixture (1:1) of **7a** (4.92 g). To a solution of **7a** (4.92 g) in acetone (50 mL) was added the Jones reagent (10 mL) at 0°C. The mixture was stirred at room temperature for 3 h. The reaction was quenched with 2-propanol (5 mL). The mixture was portioned to water and ether. The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=4.1) to give **8a** (4.39 g, 90%) as an oil. ^1H NMR ($CDCl_3$) δ 4.32–4.22 (4H, m), 2.38–2.34 (1H, m), 2.33 (3H, s), 2.09–1.97 (1H, m), 1.39 (3H, t, J=7.1 Hz), 1.38 (3H, t, J=7.1 Hz), 1.35–1.32 (1H, m), 1.30–1.25 (1H, m); ^{13}C NMR ($CDCl_3$) δ 204.9, 117.2 (dt, J_{PC}=222.1 Hz, J_{FC}=259.9 Hz), 64.1, 30.3, 24.3–23.7 (m), 23.0, 16.0, 11.5; ^{31}P NMR ($CDCl_3$) δ 6.89 (t, J_{PF}=114.6 Hz); ^{19}F NMR ($CDCl_3$) δ −50.41 (1F, ddd, J_{HF}=12.4 Hz, J_{PF}=114.6 Hz, J_{FF}=296.3 Hz), −53.51 (1F, ddd, J_{HF}=14.7, J_{PF}=114.6, J_{FF}=296.6 Hz); IR (neat) 1708, 1272 cm^{-1}; EIMS *m/z* 271 (MH^+). HRMS (EI) calcd for $C_{10}H_{17}F_2O_4P$ (M^+): 270.0833. Found: 270.0833.

Diethyl [(1*S,2*S**)-2-acetyl-1-methylcyclopropyl](difluoro)-methylphosphonate 8b.** The aldehyde **6** was treated with MeMgCl and Jones reagent as described above. The compound **8b** was obtained as an oil after column chromatography on silica gel (*n*-hexane/EtOAc=2:1) in 87% yield. ^1H NMR ($CDCl_3$) δ 4.34–4.25 (4H, m) 2.47 (1H, t, J=7.4 Hz), 2.31 (3H, s), 1.40 (3H, t, J=7.1 Hz), 1.39 (3H, t, J=7.1 Hz), 1.33–1.29 (2H, m), 1.27 (3H, s); ^{13}C NMR ($CDCl_3$) δ 204.6, 119.2 (dt, J_{PC}=218.0, J_{FC}=263.3 Hz), 64.4 (d, J_{PC}=7.7 Hz), 64.3 (d, J_{PC}=7.7 Hz), 31.8, 29.8–29.1 (m), 29.0, 16.2 (2 carbons, d, J_{PC}=5.2 Hz), 15.4, 11.5; ^{31}P NMR ($CDCl_3$) δ 7.68 (t, J_{PF}=115.7 Hz); ^{19}F NMR ($CDCl_3$) δ −51.61 (1F, dd, J_{PF}=115.7 Hz, J_{FF}=296.0 Hz), −52.70 (1F, dd, J_{PF}=115.7 Hz, J_{FF}=296.0 Hz); IR (neat) 1707, 1271 cm^{-1}; EIMS *m/z* 284 (M^+). HRMS (EI) calcd for $C_{11}H_{19}F_2O_4P$ (M^+): 284.0989. Found: 284.1010.

Diethyl difluoro[(1*S,2*S**)-2-(phenylcarbonyl)cyclopropyl]-methylphosphonate 8c.** The aldehyde **5** was treated with PhMgBr and Jones reagent in an analogous manner to that for preparation of **8a**. The compound **8c** was obtained as an oil after column chromatography on silica gel (*n*-hexane/EtOAc=4:1) in 74% yield. ^1H NMR ($CDCl_3$) δ 8.06–8.04 (2H, m), 7.61–7.47 (3H, m), 4.32–4.21 (4H, m), 3.08 (1H, ddd, J=4.5, 4.5, 8.8 Hz), 2.26–2.22 (1H, m), 1.60–1.55 (1H, m), 1.46–1.41 (1H, m), 1.37 (3H, t, J=7.1 Hz), 1.34 (3H, t, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 197.2, 137.0, 133.2, 128.5, 128.1, 117.7 (dt, J_{PC}=221.9 Hz, J_{FC}=260.1 Hz), 64.4 (d, J_{PC}=6.0 Hz), 64.3 (d, J_{PC}=4.5 Hz), 25.0 (dt, J_{PC}=19.4 Hz, J_{FC}=24.5 Hz), 19.7, 16.2 (2 carbons, d, J_{PC}=5.3 Hz), 12.3 (d, J_{PC}=6.4 Hz); ^{31}P NMR ($CDCl_3$) δ 7.61 (t, J_{PF}=113.2 Hz); ^{19}F NMR ($CDCl_3$) δ −50.11 (1F, ddd, J_{HF}=12.5 Hz, J_{PF}=113.2 Hz, J_{FF}=297.0 Hz), −52.70 (1F, ddd, J_{HF}=15.0 Hz, J_{PF}=113.2 Hz, J_{FF}=297.0 Hz); IR (neat) 1675, 1274 cm^{-1}; EIMS *m/z* 332 (M^+). Anal. Calcd for $C_{15}H_{19}F_2O_4P$: C, 54.22; H, 5.76. Found: C, 54.23; H, 5.78.

Diethyl difluoro[(1*S,2*S**)-1-methyl-2-(phenylcarbonyl)-cyclopropyl]methylphosphonate 8d.** The aldehyde **6** was treated with PhMgBr and Jones reagent in an analogous manner to that for preparation of **8a**. The compound **8d** was obtained as an oil after column chromatography on silica gel (*n*-hexane/EtOAc=4:1 to 2:1) in 86% yield. ^1H NMR ($CDCl_3$) δ 8.10–8.08 (2H, m), 7.59–7.46 (3H, m), 4.33–4.28 (4H, m), 3.17 (1H, dd, J=6.4, 8.4 Hz), 1.60–1.56 (1H, m), 1.46–1.43 (1H, m), 1.39 (3H, t, J=7.0 Hz), 1.38 (3H, t, J=7.0 Hz), 1.31 (3H, s); ^{13}C NMR ($CDCl_3$) δ 196.5, 138.1 133.0, 128.5, 128.4, 119.6 (dt, J_{PC}=217.5 Hz, J_{FC}=263.0 Hz), 64.5 (d, J_{PC}=7.0 Hz), 64.4 (d, J_{PC}=7.1 Hz), 30.5–29.8 (m), 25.8, 16.3 (2 carbons, d, J_{PC}=5.5 Hz), 15.6, 11.8; ^{31}P NMR ($CDCl_3$) δ 7.55 (t, J_{PF}=115.0 Hz); ^{19}F NMR ($CDCl_3$) δ −50.10 (1F, dd, J_{PF}=115.0 Hz, J_{FF}=296.5 Hz), −51.86 (1F, dd, J_{PF}=115.0 Hz, J_{FF}=296.5 Hz); IR (neat) 1675, 1272 cm^{-1}; EIMS *m/z* 346 (M^+). HRMS (EI) calcd for $C_{16}H_{21}F_2O_4P$ (M^+): 346.1146. Found: 346.1144.

Diethyl difluoro[(1*S,2*S**)-2-(2-phenylacetyl)cyclopropyl]methylphosphonate 8e.** The aldehyde **5** was treated with $PhCH_2MgCl$ and Jones reagent in an analogous manner to that for preparation of **8a**. The compound **8e** was obtained as an oil after column chromatography on silica gel (*n*-hexane/EtOAc=3:1) in 57% yield. ^1H NMR ($CDCl_3$) δ 7.36–7.21 (5H, m) 4.30–4.19 (4H, m), 3.89 (2H, s), 2.42–2.38 (1H, m), 2.11–1.99 (1H, m), 1.40–1.32 (1H, m), 1.37 (3H, t, J=7.0 Hz), 1.36 (3H, t, J=7.1 Hz), 1.26–1.21 (1H, m); ^{13}C NMR ($CDCl_3$) δ 205.0, 133.4 129.4, 128.6, 127.0, 117.5 (dt, J_{PC}=221.7 Hz, J_{FC}=260.3 Hz), 64.4 (d, J_{PC}=5.6 Hz), 64.3 (d, J_{PC}=5.7 Hz), 50.6, 24.7 (dt, J_{PC}=19.6, 24.5 Hz), 22.4, 16.3 (2 carbons, d, J_{PC}=5.2 Hz), 12.3 (d, J_{PC}=6.3 Hz); ^{31}P NMR ($CDCl_3$) δ 6.61 (t, J_{PF}=112.3 Hz); ^{19}F NMR ($CDCl_3$) δ −50.78 (1F, ddd, J_{HF}=11.0 Hz, J_{PF}=112.3 Hz, J_{FF}=297.0 Hz), −54.82 (1F, ddd, J_{HF}=15.5 Hz, J_{PF}=112.3 Hz, J_{FF}=297.0 Hz); IR (neat) 1706, 1273 cm^{-1}; EIMS *m/z* 346 (M^+). HRMS (EI) calcd for $C_{16}H_{21}F_2O_4P$ (M^+): 346.1146. Found: 346.1156.

Diethyl [(1*S,2*S**)-2-(2-cyclohexylacetyl)cyclopropyl](difluoro)methylphosphonate 8f.** The aldehye **5** was treated with *c*-$C_6H_{11}CH_2MgBr$ and Jones reagent in an analogous

manner to that for preparation of **8a**. The compound **8f** was obtained as an oil after column chromatography on silica gel (*n*-hexane/EtOAc=3:1) in 81% yield. ^{1}H NMR ($CDCl_3$) δ 4.31–4.22 (4H, m), 2.48 (1H, s with small split), 2.46 (1H, s with small split), 2.35–2.31 (1H, m), 2.05–1.84 (2H, m), 1.69–1.60 (5H, m), 1.38 (3H, t, J=7.1 Hz), 1.37 (3H, t, J=7.1 Hz), 1.34–1.12 (5H, m), 1.00–0.91 (2H, m); ^{13}C NMR ($CDCl_3$) δ 207.5, 117.5 (dt, J_{PC}=221.8 Hz, J_{FC}=260.0 Hz), 64.4 (d, J_{PC}=6.0 Hz), 64.3 (d, J_{PC}=6.0 Hz), 51.6, 33.8, 33.0, 26.0, 25.9, 24.3 (dt, J_{PC}=19.5, 24.3 Hz), 22.9, 16.3 (2 carbons, d, J_{PC}=5.2 Hz), 11.7 (d, J_{PC}=6.2 Hz); ^{31}P NMR ($CDCl_3$) δ 6.72 (t, J_{PF}=113.5 Hz); ^{19}F NMR ($CDCl_3$) δ −49.72 (1F, ddd, J_{HF}=12.0 Hz, J_{PF}=113.5 Hz, J_{FF}=297.0 Hz), −53.62 (1F, ddd, J_{HF}=16.0 Hz, J_{PF}=113.5 Hz, J_{FF}=297.0 Hz); IR (neat) 1702, 1274 cm^{-1}; EIMS *m/z* 352 (M^+). HRMS (EI) calcd for $C_{16}H_{27}F_2O_4P$ (M^+): 352.1615. Found: 352.1624.

Diethyl [(1*S,2*S**)-2-(3-butenoylcyclopropyl](difluoro)-methylphosphonate 8g.** The aldehyde **5** was treated with CH_2=$CHCH_2MgBr$ and Jones reagent in an analogous manner to that for preparation of **8a**. The compound **8g** was obtained as an oil after column chromatography on silica gel (*n*-hexane/EtOAc=3:1) in 19% yield. ^{1}H NMR ($CDCl_3$) δ 6.00–5.90 (1H, m), 5.24–5.16 (2H, m), 4.31–4.23 (4H, m), 3.38 (2H, td, J=1.2, 6.9 Hz), 2.38 (1H, ddd, J=4.6, 4.6, 8.9 Hz), 2.03–1.99 (1H, m), 1.38 (3H, t, J=7.1 Hz), 1.37 (3H, t, J=7.1 Hz), 1.35–1.33 (1H, m), 1.30–1.25 (1H, m); ^{13}C NMR ($CDCl_3$) δ 205.2, 129.7, 119.0, 117.4 (dt, J_{PC}=221.8 Hz, J_{FC}=260.2 Hz), 64.4 (d, J_{PC}=5.6 Hz), 64.3 (d, J_{PC}=5.2 Hz), 48.3, 24.4 (dt, J_{PC}=19.8 Hz, J_{FC}=24.4 Hz), 22.3, 16.2 (2 carbons, d, J_{PC}=5.3 Hz), 12.0; ^{31}P NMR ($CDCl_3$) δ 7.51 (t, J_{PF}=113.0 Hz); ^{19}F NMR ($CDCl_3$) δ −50.09 (1F, ddd, J_{HF}=11.5 Hz, J_{PF}=113.0 Hz, J_{FF}=297.0 Hz), −53.73 (1F, ddd, J_{HF}=15.5 Hz, J_{PF}=113.0 Hz, J_{FF}=297.0 Hz); IR (neat) 1708, 1273 cm^{-1}; EIMS *m/z* 296 (M^+). HRMS (EI) calcd for $C_{12}H_{19}F_2O_4P$ (M^+): 296.0989. Found: 296.1001.

Diethyl difluoro{(1*S,2*S**)-2-[(1*R**)-1-hydroxyethyl]cyclopropyl}methylphosphonate 9a.** To a stirred solution of **8a** (1.6 g, 5.9 mmol) in THF (70 mL) was dropwise added K-Selectride (6.5 mL of 1.0 M solution in THF) at −78°C (dry ice–acetone). The mixture was stirred at the same temperature for 20 min. MeOH (7 mL) and water (50 mL) was successively added. The mixture was extracted with $CHCl_3$. The extracts were dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (*n*-hexane/EtOAc=2:1) to give **9a** (1.24 g, 77%) as an oil. ^{1}H NMR ($CDCl_3$) δ 4.35–4.25 (4H, m), 3.27–3.20 (1H, m), 1.48–1.36 (1H, m), 1.40 (3H, t, J=7.1 Hz), 1.39 (3H, t, J=7.1 Hz), 1.33–1.23 (1H, m), 1.29 (3H, d, J=6.2 Hz), 1.10–1.05 (1H, m), 0.72–0.67 (1H, m); ^{13}C NMR ($CDCl_3$) δ 118.8 (dt, J_{PC}=220.5 Hz, J_{FC}=260.4 Hz), 69.2, 64.4 (d, J_{PC}=5.6 Hz), 23.2, 22.3, 18.5–17.8 (m), 16.2 (d, J_{PC}=3.3 Hz), 5.5; ^{31}P NMR ($CDCl_3$) δ 8.28 (t, J_{PF}=115.0 Hz), 7.73 (t, J_{PF}=116.6 Hz, for **10a**); ^{19}F NMR ($CDCl_3$) δ −46.69 (1F, ddd, J_{HF}=7.5 Hz, J_{PF}=115.0 Hz, J_{FF}=292.5 Hz), −57.13 (1F, ddd, J_{HF}=20.7 Hz, J_{PF}=115.0 Hz, J_{FF}=292.9 Hz); IR (neat) 3439, 1259 cm^{-1}; EIMS *m/z* 273 (MH^+). Anal. Calcd for $C_{10}H_{19}F_2O_4P$: C, 44.12; H, 7.04. Found. C, 44.51; H, 7.03.

Diethyl difluoro{(1*S,2*S**)-[(1*R**)-1-hydroxyethyl]-1-methylcyclopropyl}methylphosphonate 9b.** The ketone **8b** (1.42 g, 5.0 mmol) was treated with K-Selectride (5.5 mmol) as described as above. After column chromatography (SiO_2), *n*-hexane/EtOAc=2:1), diastereomerically pure **9b** (803 mg) was obtained as an oil in 57% yield. ^{1}H NMR ($CDCl_3$) δ 4.32–4.24 (4H, m), 3.48–3.41 (1H, m), 1.39 (3H, s), 1.39 (3H, t, J=6.6 Hz), 1.38 (3H, t, J=6.6 Hz), 1.30 (3H, d, J=6.2 Hz), 1.27–1.24 (2H, m), 0.36–0.32 (1H, m); ^{13}C NMR ($CDCl_3$) δ 120.3 (dt, J_{PC}=215.3 Hz, J_{FC}=264.6 Hz), 67.2, 64.6 (d, J_{PC}=6.7 Hz), 64.2 (d, J_{PC}=7.4 Hz), 28.1, 23.1–22.5 (m), 22.8, 16.2 (2 carbons d, J_{PC}=5.4 Hz), 13.8, 13.2; ^{31}P NMR ($CDCl_3$) δ 9.15 (t, J_{PF}=116.7 Hz), 8.17 (t, J_{PF}=118.9 Hz for **10b**); ^{19}F NMR ($CDCl_3$) δ −49.89 (1F, dd, J_{PF}=116.7 Hz, J_{FF}=289.9 Hz), −56.20 (1F, dd, J_{PF}=116.7 Hz, J_{FF}=289.9 Hz); IR (neat) 3455, 1260 cm^{-1}; EIMS *m/z* 285 (M^+−H). Anal. Calcd for $C_{11}H_{21}F_2O_4P$: C, 46.15; H, 7.39. Found: C, 46.36; H, 7.49.

Diethyl difluoro{(1*S,2*S**)-2-[(*S**)-hydroxy(phenyl)methyl]-cyclopropyl}methylphosphonate 9c.** The ketone **8c** (1.13 g, 3.4 mmol) was treated with K-Selectride (6.8 mmol) in an analogous manner to that for preparation of **9a**. Diastereomerically pure **9c** (735 mg) was obtained as an oil after column chromatography (SiO_2, *n*-hexane/EtOAc=1:1) in 6.5% yield. ^{1}H NMR ($CDCl_3$) δ 7.43–7.41 (2H, m), 7.37–7.28 (3H, m), 4.35–4.27 (4H, m), 4.14 (1H, d, J=8.4 Hz), 1.67–1.53 (2H, m), 1.41 (3H, t, J=7.1 Hz), 1.39 (3H, t, J=7.1 Hz), 1.17–1.12 (1H, m), 0.92–0.87 (1H, m); ^{13}C NMR ($CDCl_3$) δ 143.0, 128.3, 127.6, 125.9, 118.8 (dt, J_{PC}=221.7 Hz, J_{FC}=261.0 Hz), 76.2, 64.7 (d, J_{PC}=6.7 Hz), 64.6 (d, J_{PC}=6.9 Hz), 23.9, 19.9–19.2 (m), 16.4 (d, J_{PC}=3.2 Hz), 16.3 (d, J_{PC}=4.9 Hz), 6.4; ^{31}P NMR ($CDCl_3$) δ 9.01 (t, J_{PF}=114.4 Hz), 8.61 (t, J_{PF}=115.8 Hz for **10c**); ^{19}F NMR ($CDCl_3$) δ −46.79 (1F, dd, J_{PF}=114.4 Hz, J_{FF}=293.0 Hz), −57.62 (1F, ddd, J_{HF}=18.8 Hz, J_{PF}=114.4 Hz, J_{FF}=293.0 Hz); IR (neat) 3421, 1260 cm^{-1}; EIMS *m/z* 334 (M^+). Anal. Calcd for $C_{15}H_{21}F_2O_4P$: C, 53:89; H, 6.33. Found: C, 54.04; H, 6.35.

Diethyl difluoro{(1*S,2*S**)-[(*S**)-1-hydroxy(phenyl)methyl]-1-methylcyclopropyl}methylphosphonate 9d.** The ketone **8c** (585 mg, 1.7 mmol) was treated with K-Selectride (3.4 mmol) in an analogous manner to that for preparation of **9a**. Diastereomerically pure **9d** (479 mg) was obtained as an oil in 82% yield after column chromatography (SiO_2, *n*-hexane/EtOAc=1:1). ^{1}H NMR ($CDCl_3$) δ 7.46–7.27 (5H, m), 4.35–4.23 (5H, m), 1.54 (3H, s), 1.52–1.47 (1H, m), 1.42 (3H, t, J=7.1 Hz), 1.39 (3H, t, J=7.0 Hz), 1.36–1.32 (1H, m), 0.62–0.59 (1H, m); ^{13}C NMR ($CDCl_3$) δ 144.0, 128.3, 127.3, 125.7, 121.0 (dt, J_{PC}=214.8 Hz, J_{FC}=265.3 Hz), 73.3, 64.9 (d, J_{PC}=6.7 Hz), 64.4 (d, J_{PC}=7.5 Hz), 29.1 (d, J_{PC}=4.6 Hz), 23.7 (td, J_{FC}=19.1, J_{PC}=24.8 Hz), 16.3 (2 carbons, d, J_{PC}=5.5 Hz), 14.9 (t, J_{FC}=6.6 Hz), 13.5 (d, J_{PC}=4.3 Hz); ^{31}P NMR ($CDCl_3$) δ 9.25 (t, J_{PF}=117.0 Hz), 8.02 (t, J_{PF}=117.9 Hz for **10d**); ^{19}F NMR ($CDCl_3$) δ −50.06 (1F, dd, J_{PF}=117.0, J_{FF}=290.0 Hz), −56.72 (1F, dd, J_{PF}=117.0, J_{FF}=290.0 Hz); IR (neat) 3433, 1259 cm^{-1}; EIMS *m/z* 348 (M^+). Anal. Calcd for $C_{16}H_{23}F_2O_4P$: C, 55.18; H, 6.66. Found: C, 55.48; H, 6.72.

Diethyl difluoro{(1*S,2*S**)-2-[(1*R**)-1-hydroxy-2-phenylethyl]cyclopropyl}methylphosphonate 9e.** The ketone **8e** (361 mg, 1.04 mmol) was treated with K-Selectride (2.08 mmol) in an analogous manner to that for preparation of **9a**. Diastereomerically pure **9e** (186 mg) was obtained as an oil after column chromatography (SiO_2, *n*-hexane/EtOAc=1:1) in 51% yield. ^{1}H NMR ($CDCl_3$) δ 7.31–7.19 (5H, m), 4.31–4.23 (4H, m), 3.32 (1H, dt J=6.6, 6.6 Hz), 2.90 (2H, d, J=6.6 Hz), 1.48–1.40 (1H, m), 1.38 (3H, t, J=7.1 Hz), 1.37 (3H, t, J=7.1 Hz), 1.34–1.30 (1H, m), 1.04–0.99 (1H, m), 0.61–0.56 (1H, m); ^{13}C NMR ($CDCl_3$) δ 138.1, 129.5, 128.3, 126.3, 118.9 (dt, J_{PC}=220.7 Hz, J_{FC}=259.5 Hz), 74.7, 64.6 (d, J_{PC}=6.7 Hz), 64.5 (d, J_{PC}=6.9 Hz), 43.6, 21.7 (d, J_{PC}=5.4 Hz), 18.7–18.1 (m), 16.4 (2 carbons), 6.3; ^{31}P NMR ($CDCl_3$) δ 8.97 (t, J_{PF}=115.3 Hz), 8.32 (t, J_{FF}=293.0 Hz), −56.39 (1F, ddd, J_{HF}=19.8 Hz, J_{PF}=115.3 Hz, J_{FF}=293.0 Hz); IR (neat) 3429, 1260 cm^{-1}; EIMS *m/z* 347 (M^+-H). HRMS (EI) calcd for $C_{16}H_{23}F_2O_4P$ (M^+-H): 347.1224. Found: 347.1228.

Diethyl {(1*S,2*S**)-2-[(1*R**)-2-cyclohexyl-1-hydroxyethyl]-cyclopropyl}(difluoro)methylphosphonate 9f.** The ketone **8f** (880 mg, 2.5 mmol) was treated with K-Selectride (5.0 mmol) in an analogous manner to that for preparation of **9a**. Diastereomerically pure **9f** (433 mg) was obtained as an oil after column chromatography (SiO_2, *n*-hexane/EtOAc=1:1) in 49% yield. ^{1}H NMR ($CDCl_3$) δ 4.33–4.24 (4H, m), 3.17–3.12 (1H, m), 1.78–1.75 (1H, m), 1.70–1.63 (4H, m), 1.57–1.49 (2H, m), 1.39 (3H, t, J=7.1 Hz), 1.38 (3H, J=7.0 Hz), 1.30–1.18 (4H, m), 1.16–1.06 (2H, m), 0.98–0.80 (2H, m), 0.73–0.68 (1H, m); ^{13}C NMR ($CDCl_3$) δ 118.9 (dt, J_{PC}=220.7 Hz, J_{FC}=260.5 Hz), 71.4, 64.6 (d, J_{PC}=8.3 Hz), 64.5 (d, J_{PC}=7.4 Hz), 44.9, 34.2, 33.8, 32.9, 26.6, 26.3, 26.1, 22.9, 18.9–18.2 (m), 16.4 (2 carbons), 6.1; ^{31}P NMR ($CDCl_3$) δ 8.20 (t, J_{PF}=115.4 Hz), 7.49 (t, J_{PF}=116.9 Hz for **10f**); ^{19}F NMR ($CDCl_3$) δ −46.73 (1F, ddd, J_{HF}=7.0 Hz, J_{PF}=115.4 Hz, J_{FF}=292.0 Hz), −56.96 (1F, ddd, J_{HF}=20.0 Hz, J_{PF}=115.4 Hz, J_{Ff}=292.0 Hz); IR (neat) 3444, 1261 cm^{-1}; EIMS *m/z* 354 (M^+). Anal. Calcd for $C_{16}H_{29}F_2O_4P$: C, 54.23; H, 8.25. Found: C, 54.24; H, 8.14.

Diethyl difluoro{(1*S,2*S**)-2-[(1*R**)-1-hydroxy-3-butenyl]-cyclopropyl}methylphosphonate 9g.** The ketone **8g** (182 mg, 0.62 mmol) was treated with K-Selectride (1.23 mmol) in an analogous manner to that for preparation of **9a**. Diastereomerically pure **9g** (115 mg) was obtained as an oil after column chromatography (SiO_2, *n*-hexane/EtOAc=1:1) in 63% yield. ^{1}H NMR ($CDCl_3$) δ 5.94–5.83 (1H, m), 5.17–5.09 (2H, m), 4.33–4.24 (4H, m), 3.15 (1H, dt, J=6.6, 6.6 Hz), 2.44–2.30 (2H, m), 1.48–1.43 (1H, m), 1.40 (3H, t, J=7.1 Hz), 1.39 (3H, t, J=7.1 Hz), 1.33–1.29 (1H, m), 1.11–1.06 (1H, m), 0.77–0.72 (1H, m); ^{13}C NMR ($CDCl_3$) δ 134.4, 118.8 (dt, J_{PC}=222.2 Hz, J_{FC}=259.5 Hz), 117.4, 72.6, 64.5 (d, J_{PC}=7.9 Hz), 64.4 (d, J_{PC}=7.7 Hz), 41.5, 21.5, 18.4–17.7 (m), 16.3 (d, J_{PC}=4.9 Hz), 16.2 (d, J_{PC}=4.9 Hz), 6.0; ^{31}P NMR ($CDCl_3$) δ 8.96 (t, J_{PF}=115.0 Hz), 8.30 (t, J_{PF}=116.0 Hz for **10g**); ^{19}F NMR ($CDCl_3$) δ −48.21 (1F, ddd, J_{HF}=9.0 Hz, J_{PF}=115.0 Hz, J_{FF}=293.0 Hz), −57.32 (1F, ddd, J_{HF}=20.0 Hz, J_{PF}=115.0 Hz, J_{FF}=293.0 Hz); IR (neat) 3435, 1261 cm^{-1}; EIMS *m/z* 299 (MH^+). HRMS (EI) calcd for $C_{12}H_{20}F_2O_4P$ (M^+−H): 297.1067. Found: 297.1073.

Diethyl difluoro{(1*S,2*S**)-2-[(1*S**)-1-hydroxyethyl]cyclopropyl}methylphosphonate 10a.** *Method A:* To a solution of **8a** (308 mg, 1.1 mmol) in THF (15 mL) was added DIBAL-H (0.95 M in hexane, 1.80 mL, 1.7 mmol) slowly at −78°C. The mixture was stirred at the same temperature for 1 h and then poured into H_2O. The resulting mixture was extracted with EtOAc. The extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel. Elution with *n*-hexane/EtOAc=5:1 gave the starting **8a** (98 mg). Successive eluation with *n*-hexane/EtOAc=2:1 gave **10a** (38 mg, 12%): ^{1}H NMR ($CDCl_3$) δ 4.33–4.24 (4H, m), 3.53–3.47 (1H, m), 1.47–1.36 (2H, m), 1.39 (6H, t, J=7.1 Hz), 1.27 (3H, d, J=6.3 Hz), 1.03–0.98 (1H, m), 0.81–0.76 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.8 (dt, J_{CP}=222.6 Hz, J_{CF}=259.1 Hz), 68.4, 64.3 (2 carbons, J_{CP}=7.5 Hz, d, J_{CP}=9.1 Hz), 22.5, 22.2, 17.3 (dt, J_{CP}=19.1 Hz, J_{CF}=24.2 Hz), 16.2 (d, J_{CP}=4.9 Hz), 5.7; ^{31}P NMR ($CDCl_3$) δ 7.73 (t, J_{PF}=116.6 Hz); ^{19}F NMR ($CDCl_3$) δ −49.98 (1F, ddd, J_{FF}=295.1 Hz, J_{FP}=116.6 Hz, J_{HH}=12.4 Hz), −52.81 (1F, ddd, J_{FF}=295.1 Hz, J_{FP}=116.6 Hz, J_{FH}=15.1 Hz); IR (neat) 3432, 1260 cm^{-1}; EIMS *m/z* 273 (M^++1). HRMS (EI) calcd for $C_{10}H_{18}F_2O_3P$ (M^+−OH): 255.0962. Found: 255.0964. *Method B:* The benzoate **13** (2.26 g, 6.0 mmol) in MeOH (230 mL) was treated with 1N NaOH (36 mL, 36 mmol) for 15 h at 25°C. Half volume of the solvent was evaporated and then water was added. The mixture was extracted with $CHCl_3$ and the extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (*n*-hexane/EtOAc=2:1) to give **10a** (1.07 g, 67%) as an oil. The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) was identical to that of the authentic sample prepared by Method A.

(1*S)-1-{(1*S**,2*S**)-2-[Diethoxyphosphoryl)(difluoromethyl]-cyclopropyl}ethyl benzoate 13.** To a solution of alcohol **9a** (2.72 g, 10 mmol), benzoic acid (1.59 g, 13 mmol) and Ph_3P (3.93 g) in ether (90 mL) was added diethyl azodicarboxylate (40% in toluene, 6.53 mL, 15 mmol) under ice-cooling. The mixture was stirred at 25°C for 15 h. Volatile component of the mixture was evaporated. The residue was chromatographed on silica gel (*n*-hexane/EtOAc=8:1) to give **13** (3.60 g, 96%) as an oil. ^{1}H NMR ($CDCl_3$) δ 8.06–8.02 (2H, m), 7.58–7.54 (1H, m), 4.81–4.74 (1H, m), 4.32–4.22 (4H, m), 1.62–1.49 (2H, m), 1.46 (3H, d, J=6.3 Hz), 1.38 (6H, t, J=7.1 Hz), 1.09–1.02 (1H, m), 1.00–0.95 (1H, m); ^{13}C NMR ($CDCl_3$) δ 165.8, 132.8, 130.3, 129.4, 128.2, 118.4 (dt, J_{CP}=222.6 Hz, J_{CF}=259.2 Hz), 72.7, 64.3 (with small splits), 20.2, 19.6, 18.2 (dt, J_{CP}=18.9 Hz, J_{CF}=24.5 Hz), 16.3, 7.1; ^{31}P NMR ($CDCl_3$) δ 7.42 (t, J_{PF}=116.5 Hz); ^{19}F NMR ($CDCl_3$) δ −51.51 (2F, ddd, J_{FP}=116.5 Hz, J_{FH}=13.9 Hz, J_{FH}=6.8 Hz); IR (neat) 1716, 1272 cm^{-1}; EIMS *m/z* 376 (M^+). Anal. Calcd for $C_{17}H_{23}F_2O5P$: C, 54.25; H, 6.16. Found: C, 53.91; H, 5.96.

Diethyl {(1*S,2*S**)-2-[(1*S**)-1-(6-chloro-9*H*-purin-9-yl)ethyl]-cyclopropyl}(difluoro)methylphosphonate 11a.** To a solution of **9a** (1.03 g, 3.8 mmol), 6-chloropurine (761 mg, 4.9 mmol) and Ph_3P (1.49 g, 5.7 mmol) in THF (35 mL) was added diethyl azodicarboxylate (40% solution in toluene, 2.47 mL, 5.7 mmol) at room temperature. The mixture was stirred for 14 h at room temperature. Volatile

component of the mixture was removed in vacuo. The residue was chromatographed on silica gel. Elution with $CHCl_3$ gave **11a** (657 mg, 43%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.72 (1H, s, C2-*H*), 8.26 (1H, s, C8-*H*), 4.33–4.26 (4H, m), 4.24–4.17 (1H, m), 1.89–1.81 (1H, m), 1.78 (3H, d, J=6.9 Hz), 1.67–1.60 (1H, m), 1.40 (6H, t with small splits, J=7.0 Hz), 1.06–1.01 (1H, m), 0.93–0.88 (1H, m); ^{13}C NMR ($CDCl_3$) δ 151.6, 151.4, 150.8, 143.1, 131.6, 118.0 (dt, J_{PC}=222.0 Hz, J_{FC}=259.8 Hz), 64.5 (2 carbons, d, J_{PC}=5.7 Hz), 55.3, 20.7, 20.5–20.2 (m), 20.0, 16.3 (d with small splits, J_{PC}=2.9 Hz), 7.7; ^{31}P NMR ($CDCl_3$) δ 6.96 (t, J_{PF}=113.3 Hz); ^{19}F NMR ($CDCl_3$) δ −51.39 (1F, ddd, J_{HF}=13.6 Hz, J_{PF}=113.3 Hz, J_{FF}=296.6 Hz), −52.32 (1F, ddd, J_{HF}=13.9 Hz, J_{PF}=113.3 Hz, J_{FF}=296.6 Hz); IR (neat) 1591, 1558, 1268 cm^{-1}; EIMS *m*/*z* 408 (M^+). Anal. Calcd for $C_{15}H_{20}ClF_2N_4O_3P$: C, 44.07; H, 4.93; N, 13.71. Found: C, 43.99; H, 5.11; N, 13.55. Successive elution with $CHCl_3$/MeOH=400:1 gave the *N*-7 isomer (302 mg, 20%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (1H, s, C2-*H*), 8.55 (1H, s, C8-*H*).

Diethyl {(1*S,2*S**)-2-[(1*R**)-1-(6-chloro-9*H*-purin-9-yl)ethyl]-1-methylcyclopropyl}(difluoro)methylphosphonate 11b.** The alcohol **9b** (572 mg, 2.0 mmol) was coupled with 6-chloropurine in an analogous manner to that for preparation of **11a**. Column chromatography of the crude materials on silica gel (*n*-hexane/EtOAc=3:1 to 1:1) gave **11b** (363 mg, 43%): mp 115–118°C; ^{1}H NMR ($CDCl_3$) δ 8.72 (1H, s), 8.28 (1H, s), 4.49–4.41 (1H, m), 4.35–4.24 (4H, m), 1.88–1.82 (1H, m), 1.79 (3H, d, J=6.9 Hz), 1.55 (3H, s), 1.42 (3H, t, J=7.1 Hz), 1.41 (3H, t, J=7.1 Hz), 1.19–1.16 (1H, m), 0.54–0.50 (1H, m); ^{13}C NMR ($CDCl_3$) δ 151.6, 150.9, 143.2, 131.7, 128.4, 119.5 (dt, J_{PC}=217.9 Hz, J_{FC}=263.0 Hz), 64.5 (d, J_{PC}=6.8 Hz), 64.4 (d, J_{PC}=6.9 Hz), 52.4, 25.1 (d, J_{PC}=6.8 Hz), 24.8–24.1 (m), 21.4, 16.3 (2 carbons, d, J_{PC}=5.3 Hz), 14.9, 13.3; ^{31}P NMR ($CDCl_3$) δ 7.57 (t, J_{PF}=116.0 Hz); ^{19}F NMR ($CDCl_3$) δ −51.36 (1F, dd, J_{PF}=116.0 Hz, J_{FF}=297.0 Hz), −53.73 (1F, dd, J_{PF}=116.0 Hz, J_{FF}=297.0 Hz); IR (KBr) 1589, 1570, 1269 cm^{-1}; EIMS *m*/*z* 423 (MH^+). Anal. Calcd for $C_{16}H_{22}ClF_2N_4O_3P$: C, 45.45; H, 5.24; N, 13.25. Found: C, 45.49; H, 5.28; N, 13.15.

Diethyl {(1*S,2*S**)-2-[(*S**)-1-(6-chloro-9*H*-purin-9-yl)-(phenyl)methyl]-1-methylcyclopropyl}(difluoro)methylphosphonate 11d.** The alcohol **9d** (696 mg, 2.0 mmol) was coupled with 6-chloropurine in an analogous manner to that for preparation of **11a**. Column chromatography of the crude materials on silica gel eluted by *n*-hexane/EtOAc=1:1 gave **11d** (309 mg, 32%): mp 145–147°C, ^{1}H NMR ($CDCl_3$) δ 8.75 (1H, s), 8.16 (1H, s), 7.46–7.36 (5H, m), 5.55 (1H, d, J=10.9 Hz), 4.27–4.13 (4H, m), 2.42–2.36 (1H, m), 1.50 (3H, s), 1.34 (3H, t, J=7.1 Hz), 1.33 (3H, t, J=7.1 Hz), 1.29–1.25 (1H, m), 0.78–0.75 (1H, m); ^{13}C NMR ($CDCl_3$) δ 152.0, 151.7, 151.1, 143.9, 137.5, 131.4, 129.2, 128.9, 127.0, 119.7 (dt, J_{PC}=218.0 Hz, J_{FC}=262.9 Hz), 64.4 (d, J_{PC}=8.0 Hz), 64.3 (d, J_{PC}=7.8 Hz), 58.8, 25.5–24.9 (m), 22.9, 16.3 (2 carbons, d, J_{PC}=5.1 Hz), 15.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 6.47 (t, J_{PF}=115.0 Hz); ^{19}F NMR ($CDCl_3$) δ −50.22 (1F, dd, J_{PF}=115.0 Hz, J_{FF}=298.0 Hz), −52.63 (1F, dd, J_{PF}=115.0 Hz, J_{FF}=298.0 Hz); IR (KBr) 1592, 1561, 1262 cm^{-1}; FABMS *m*/*z* 485 (MH^+). Anal. Calcd for $C_{21}H_{24}ClF_2N_4O_3P$: C, 52.02; H, 4.99; N, 11.56. Found: C, 52.16; H, 4.86; N, 11.53.

Crystal data for compound 11d

X-ray crystal data of **11d** were collected by MAC-Science DIPlabo diffractometer. The structure was solved by a direct method using SIR92 (Altomare, 1994)[11] and refined with a full matrix least-squares method. Molecular formula=$C_{21}H_{24}ClF_2N_4O_3P$, M_r=484.871, monoclinic, space group=$P2_1/c$, a=12.4540 (4) Å, b=11.0420 (5) Å, c=16.9750 (5) Å, β=100.834 (3)°, V=2292.7 (1) Å^3, Z=4, D_x=1.405 Mg m^{-3}, (Mo-Cu)=0.71073 Å, μ= 0.28 mm^{-1}, T=180 K, R=0.043 over 4390 independent reflections.

Diethyl {(1*S,2*S**)-2-[(1*R**)-1-(6-chloro-9*H*-purin-9-yl)-2-phenylethyl]cyclopropyl}(difluoro)methylphosphonate 11e.** The alcohol **9e** (696 mg, 2.0 mmol) was coupled with 6-chloropurine in an analogous manner to that for preparation of **11a**. Column chromatography of the crude materials on silica gel eluted by *n*-hexane/EtOAc=1:1 gave **11e** (81 mg, 8.4%): mp 146–148°C; ^{1}H NMR ($CDCl_3$) δ 8.74 (1H, s, C2-*H*), 8.08 (1H, s, C8-*H*), 7.71–7.69 (1H, m), 7.33–7.27 (2H, m), 7.21–7.18 (1H, m), 5.60 (1H, d, J=8.8 Hz), 4.27–4.16 (4H, m), 2.27–2.21 (1H, m), 1.70–1.63 (1H, m), 1.55 (2H, s), 1.34 (3H, t, J=7.0 Hz), 1.33 (3H, t, J=7.0 Hz), 1.17–1.14 (2H, m); ^{13}C NMR ($CDCl_3$) δ 152.0, 151.6, 143.7, 136.6, 134.2, 131.2, 129.2, 127.0, 126.7, 118.3 (dt, J_{PC}=221.7 Hz, J_{FC}=260.2 Hz), 64.5 (d, J_{PC}=6.7 Hz), 64.4 (d, J_{PC}=6.7 Hz), 57.8, 20.2–19.5 (m), 19.1, 18.4, 16.3 (2 carbons, d, J_{PC}=5.3 Hz), 8.6; ^{31}P NMR ($CDCl_3$) δ 7.48 (t, J_{PF}=113.8 Hz); ^{19}F NMR ($CDCl_3$) δ −46.55 (1F, ddd, J_{HF}=9.0 Hz, J_{PF}=113.8 Hz, J_{FF}=296.0 Hz), −55.48 (1F, ddd, J_{HF}=18.0 Hz, J_{PF}=113.8 Hz, J_{FF}=296.0 Hz); IR (KBr) 1584, 1558, 1267 cm^{-1}; EIMS *m*/*z* 484 (M^+). Anal. Calcd for $C_{21}H_{24}F_2ClN_4O_3P$: C, 52.02; H, 4.99; N, 11.56. Found: C, 52.32; H, 5.11; N, 11.46. The signals due to the C2-H and C8-H of the *N*-7 isomer were observed at δ 8.75 and 8.02, respectively, in the ^{1}H NMR spectrum (300 MHz, $CDCl_3$).[10]

Diethyl {(1*S,2*S**)-2-[(1*R**)-1-(6-chloro-9*H*-purin-9-yl)-2-cyclohexylethyl]cyclopropyl}(difluoro)methylphosphonate 11f.** The alcohol **9f** (354 mg, 1.0 mmol) was coupled with 6-chloropurine in an analogous manner to that for preparation of **11a**. Column chromatography of the crude materials on silica gel eluted by *n*-hexane/EtOAc=1:1 gave **11f** (112 mg, 23%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (1H, s), 8.19 (1H, s), 4.34–4.25 (4H, m), 4.14 (1H, dt, J=4.3, 10.2 Hz), 2.22–2.15 (1H, m), 2.01–1.94 (1H, m), 1.89–1.82 (1H, m), 1.77–1.74 (1H, m), 1.69–1.51 (7H, m), 1.40 (3H, d, J=7.1 Hz), 1.39 (3H, t, J=7.1 Hz), 1.12–0.78 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 151.6, 150.9, 143.4, 131.5, 118.0 (dt, J_{PC}=221.9 Hz, J_{FC}=260.0 Hz), 64.5 (d, J_{PC}=7.3 Hz), 64.4 (d, J_{PC}=7.3 Hz), 57.1, 41.6, 33.7, 33.5, 32.0, 26.0, 25.7, 25.5, 21.2–20.5 (m), 20.5, 16.3 (2 carbons, d, J_{PC}=3.2 Hz), 7.6; ^{31}P NMR ($CDCl_3$) δ 7.66 (t, J_{PF}=113.8 Hz); ^{19}F NMR ($CDCl_3$) δ −50.36 (1F, ddd, J_{HF}=12.0 Hz, J_{PF}=113.8 Hz, J_{FF}=296.0 Hz), −53.02 (1F, ddd, J_{HF}=15.0 Hz, J_{PF}=113.8 Hz, J_{FF}=296.0 Hz); IR (neat) 1590, 1557, 1267 cm^{-1}; EIMS *m*/*z* 490 (M^+).

HRMS (EI) calcd for $C_{21}H_{29}ClF_2N_4O_3P$ (M^+-1): 489.1634. Found: 489.1658.

Diethyl {(1*S,2*S**)-2-[(1*R**)-1-(6-chloro-9*H*-purin-9-yl)-ethyl]cyclopropyl}(difluoro)methylphosphonate 14.** Alcohol **10a** (1.06 g, 3.9 mmol) was coupled with 6-chloropurine in an analogous manner to that for preparation of **11a**. Column chromatography of the crude materials on silica gel eluted by $CHCl_3$ gave **14** (834 mg, 53%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.73 (1H, s, C2-*H*), 8.32 (1H, s, C8-*H*), 4.26–4.19 (1H, m), 4.12–3.95 (4H, m), 1.84–1.78 (1H, m), 1.76 (3H, d, J=7.1 Hz), 1.70–1.59 (1H, m), 1.33–1.24 (1H, m), 1.26 (3H, t, J=7.1 Hz), 1.22 (3H, t, J=7.1 Hz), 0.94–0.89 (1H, m), ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 151.2, 150.3, 143.3, 131.3, 117.5 (dt, J_{CP}=223.0 Hz, J_{CF}=259.3 Hz), 64.1 (d with small splits, J_{CP}=7.7 Hz), 54.7, 21.0 (d, J_{CP}=6.2 Hz), 19.6, 19.4 (dt, J_{CP}=18.9 Hz, J_{CF}=24.6 Hz), 15.9 (d, J_{CP}=5.0 Hz), 7.6; ^{31}P NMR ($CDCl_3$) δ 6.86 (t, J_{PF}=113.4 Hz); ^{19}F NMR ($CDCl_3$) δ −50.13 (1F, ddd, J_{FH}=12.0 Hz, J_{FF}=297.4 Hz, J_{FP}=113.4 Hz), −53.55 (1F, ddd, J_{FH}=15.1 Hz, J_{FF}=297.4 Hz, J_{FP}=113.4 Hz); IR (neat) 1592, 1558, 1267 cm^{-1}; EIMS *m*/*z* 408 (M^+). Anal. Calcd for $C_{15}H_{20}ClF_2N_4O_3P$: C, 44.07; H, 4.93; N, 13.71. Found: C, 43.74; H, 5.07; N, 13.35. Successive elution with $CHCl_3$/MeOH=400:1 gave the *N*-7 isomer (305 mg, 20%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (1H, s, C2-*H*), 8.60 (1H, s, C8-*H*).

Difluoro{(1*S,2*S**)-2-[(1*S**)-1-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethyl]cyclopropyl]methylphosphonic acid 2a.** To a stirred solution of **11a** (384 mg, 0.9 mmol) in CH_2Cl_2 (6 mL) was added bromotrimethylsilane (0.62 mL, 4.7 mmol) at room temperature. The mixture was stirred for 37 h and evaporated under reduced pressure. The residue was treated with H_2O (3 mL) at room temperature for 48 h. The mixture was portioned between $CHCl_3$ and H_2O. The aqueous layer was washed with $CHCl_3$. Lyophilization of the aqueous layer gave **12a** (304 mg, 97%) as an amorphous powder. ^{1}H NMR (D_2O) δ 9.15 (1H, s), 8.21 (1H, s), 4.37–4.29 (1H, m), 1.83–1.76 (1H, m), 1.71–1.64 (1H, m), 1.61 (3H, d, J=6.9 Hz), 0.95–0.90 (1H, m), 0.81–0.76 (1H, m); ^{13}C NMR (D_2O) δ 154.3, 149.0 (with small splits), 147.0, 138.1, 119.4 (dt, J_{PC}=206.6 Hz, J_{FC}=258.6 Hz), 115.8, 57.9, 20.1 (dt, J_{PC}=18.3 Hz, J_{FC}=24.6 Hz), 19.6, 19.0, 7.6; ^{31}P NMR (D_2O) δ 4.44 (t, J_{PF}=102.6 Hz); ^{19}F NMR (D_2O) δ −38.43 (1F, ddd, J_{HF}=13.2 Hz, J_{PF}=102.6 Hz, J_{FF}=287.6 Hz), −40.24 (1F, ddd, J_{HF}=14.3 Hz, J_{PF}=102.6 Hz, J_{FF}=287.2 Hz); IR (KBr) 1711, 1572, 1188 cm^{-1}; UV(H_2O) λ_{max} 250 nm (ϵ=10057); FABMS *m*/*z* 335 (MH^+). HRMS (FAB) calcd for $C_{11}H_{14}F_2N_4O_4P$ (MH^+): 335.0721. Found: 335.0726.

Difluoro{(1*S,2*S**)-1-methyl-2-[(1*R**)-1-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethyl]cyclopropyl}methylphosphonic acid 12b.** The compound **11b** (422 mg, 1.0 mmol) was hydrolyzed in an analogous manner to that for preparation of **12a** to give **12b** (313 mg, 90%) as amorphous powder: ^{1}H NMR (CD_3OD) δ 9.42 (1H, s), 8.24 (1H, s), 4.61–4.53 (1H, m), 2.02–1.95 (1H, m), 1.78 (3H, d, J=6.8 Hz), 1.49 (3H, s), 1.16–1.12 (1H, m), 0.61–0.58 (1H, m); ^{31}P NMR (CD_3OD) δ 6.23 (t, J_{PF}=112.6 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ −52.49 (1F, dd, J_{PF}=112.6 Hz, J_{FF}=294.5 Hz), −54.51 (1F, dd, J_{PF}=112.6 Hz, J_{FF}=294.5 Hz); IR (KBr) 1716, 1569, 1176 cm^{-1}; FABMS *m*/*z* 349 (MH^+). HRMS (FAB) calcd for $C_{12}H_{16}F_2N_4O_4P$ (MH^+): 349.0877. Found: 349.0897.

Difluoro{(1*S,2*S**)-2-[(1*R**)-1-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)-2-phenylethyl]cyclopropyl}methylphosphonic acid 12e.** The compound **11e** (484 mg, 1.0 mmol) was hydrolyzed in an analogous manner to that for preparation of **12a** to give **12e** (250 mg, 61%) as amorphous powder: ^{1}H NMR (CD_3OD) δ 9.30 (1H, s), 8.26 (1H,s), 7.55–7.52 (1H, m), 7.27–7.21 (4H, m), 5.94–5.83 (1H, m), 2.39–2.35 (2H, m), 1.85–1.78 (1H, m), 1.28–1.15 (2H, m), 1.04–0.99 (1H, m); ^{31}P NMR (CD_3OD) δ 6.13 (t, J_{PF}=109.4 Hz); ^{19}F NMR (CD_3OD) δ −50.19 (1F, ddd, J_{HF}=10.0 Hz, J_{PF}=109.4 Hz, J_{FF}=293.6 Hz), −57.10 (1F, ddd, J_{HF}=18.0 Hz, J_{PF}=109.4 Hz, J_{FF}=293.6 Hz); IR (KBr) 1685, 1578, 1161 cm^{-1}; FABMS *m*/*z* 411 (MH^+). HRMS (FAB) calcd for $C_{17}H_{18}F_2N_4O_4P$ (MH^+): 411.1034. Found: 411.1007.

{(1*S,2*S**)-2-[(1*R**)-2-Cyclohexyl-1-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethyl]cyclopropyl}(difluoro)methylphosphonic acid 12f.** The compound 11f (488 mg, 1.0 mmol) was hydrolyzed in an analogous manner to that for preparation of **12a** to give **12f** (120 mg, 29%) as amorphous powder: ^{1}H NMR (CD_3OD) δ 9.50 (1H, s), 8.27 (1H, s), 4.38 (1H, dt, J=5.2, 9.8 Hz), 2.27–2.19 (1H, m), 2.08–1.94 (2H, m), 1.83–1.73 (2H, m), 1.67–1.61 (5H, m), 1.23–0.85 (7H, m); ^{31}P NMR (CD_3OD) δ 6.28 (t, J_{PF}=110.3 Hz); ^{19}F NMR (CD_3OD) δ −53.94 (1F, ddd, J_{HF}=13.3 Hz, J_{PF}=110.5 Hz, J_{FF}=294.0 Hz), −55.26 (1F, ddd, J_{HF}=13.8 Hz, J_{PF}=110.5 Hz, J_{FF}=294.0 Hz); IR (KBr) 1717, 1569, 1185 cm^{-1}; FABMS *m*/*z* 417 (MH^+). HRMS (FAB) calcd for $C_{17}H_{24}F_2N_4O_4P$ (MH^+): 417.1503. Found: 417.1498.

Difluoro{(1*S,2*S**)-2-[(1*R**)-1-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethyl]cyclopropyl}methylphosphonic acid 15.** The compound **14** (408 mg, 1.0 mmol) was hydrolyzed in an analogous manner to that for preparation of **12a** to give **15** (323 mg, 97%) as amorphous powder: ^{1}H NMR (D_2O) δ 9.10 (1H, s), 8.20 (1H, s), 4.26–4.18 (1H, m), 1.79–1.72 (1H, m), 1.63 (3H, d, J=6.9 Hz), 1.57–1.45 (1H, m), 1.14–1.09 (1H, m), 0.92–0.87 (1H, m); ^{13}C NMR (100 MHz, D_2O) δ 154.3, 148.9 (with small splits), 147.1,138.1, 119.5 (dt, J_{CP}=206.6 Hz, J_{CF}=257.3 Hz), 115.7, 58.1, 20.5, 19.6 (dt, J_{CP}=18.3 Hz, J_{CF}=24.6 Hz), 18.9, 7.6; ^{31}P NMR (D_2O) δ 4.38 (t, J_{PF}=102.8 Hz); ^{19}F NMR (D_2O) δ −39.01 (1F, ddd, J_{FH}=13.9 Hz, J_{FF}=288.0 Hz, J_{FP}=102.8 Hz), −40.34 (1F, ddd, J_{FH}=13.9 Hz, J_{FF}=288.0 Hz, J_{FP}=102.8 Hz); IR (KBr) 1711, 1572, 1189 cm^{-1}; UV (H_2O) λ_{max} 251 nm (ϵ=11854); FABMS *m*/z335 (MH^+); HRMS (FAB) calcd for $C_{11}H_{14}F_2N_4O_4P$ (MH^+): 335.0721. Found: 335.0726.

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