# Convenient Synthesis of Cyclopropylalkanol Derivatives Possessing a Difluoromethylenephosphonate Group at the Ring

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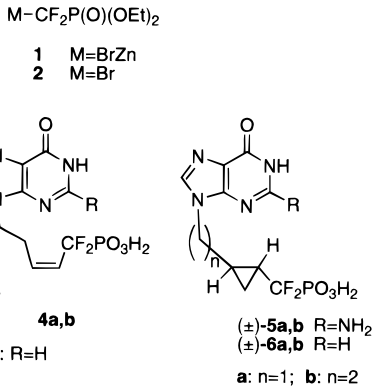
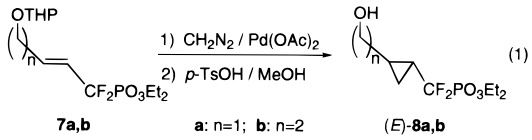
## Introduction

Interest is growing in the development of general methods that allow the synthesis of compounds in which the difluoromethylenephosphonate group is borne within a functionalized array.[1] Recently, we have developed a facile method for incorporating a difluoromethylenephosphonate group onto an $sp^2$ carbon atom through copper-catalyzed cross-coupling reaction of [(diethoxyphosphoryl)-difluoromethyl]zinc bromide **1**, generated from diethyl bromodifluoromethylphosphonate **2** and zinc in dimethylformamide (DMF) or dimethylacetamide (DMA), with iodoalkenes and iodobenzene derivatives.[2] The coupling reactions with iodoalkenes allow us to synthesize a series of novel acyclic nucleotide analogues **3a,b** and **4a,b** as well as the related methano analogues (±)-**5a,b** and (±)-**6a,b**.[2c,e] In our biological evaluation of these nucleotide analogues for purine nucleoside phosphorylases (PNPs), we discovered that the cyclopropylalkyl spacers connecting the purine base and the difluoromethylphosphonic acid within the functionalized array of (±)-**6a,b** constitute their good binding affinity ($K_i$ = 5.4−8.8 nM) to the PNP purified from *Cellulomonas* sp.[2e]

The functionalized cyclopropanes (*E*)-**8a,b**, required for the synthesis of the methano analogues (±)-**5a,b** and (±)-**6a,b**, were previously prepared through Pd(II)-catalyzed cyclopropanation reaction of the allylic α,α-difluorophosphonates **7a,b** with a large excess of diazomethane, followed by deprotection (eq 1).[2c,e] However, the toxicity and explosive character of diazomethane have hampered

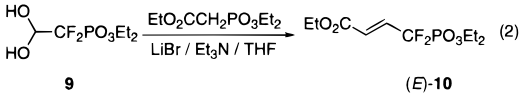



the large-scale preparation of these useful functionalized cyclopropanes (*E*)-**8a,b** and the analogous compounds by this route. In this paper, we now disclose that these species as well as the related compounds can be conveniently prepared by an alternative method which involves sulfur-ylide-induced cyclopropanation of enoates bearing the difluoromethylenephosphonate group, followed by chemoselective reduction of the carboxyester function.




## Results and Discussion

**Copper(I)-Catalyzed Coupling Reaction of [(Diethoxyphosphoryl)difluoromethyl]zinc Bromides 1 with β-Iodoenoates and 4-Iodobut-3-en-2-one.** (*E*)-Enoate (*E*)-**10**, a suitable precursor for the preparation of (*E*)-**8a** through the cyclopropanation with sulfur-ylides, has been previously prepared by Percy using a Wadsworth−Horner−Emmons reaction of the masked aldehyde **9** with triethyl phosphonoacetate (eq 2).[3] However, we envisioned that (*E*)-**10** and the related compounds,




including the stereoisomers, would be more readily prepared by an application of the cross-coupling reaction of the zinc reagent **1** with β-iodoalkenoates or β-iodoalkenones. Therefore, we initially examined the cross-coupling reaction of **1** with β-iodoalkenoates (*E*)-**11**, (*Z*)-**11**, (*Z*)-**12**, and (*E*)-**13**, as well as the related (*E*)-4-iodobut-3-en-2-one (*E*)-**14**. These substrates were prepared stereoselectively by the literature procedures[4] or a sequential oxidation and esterification of the corresponding known iodoalkenols.[5] The results of this coupling study are summarized in Table 1.

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(1) (a) Berkowitz, D. B.; Euggen, M.; Shen, Q.; Sloss, D. G. *J. Org. Chem*. **1993**, *58*, 6174. (b) Berkowitz, D. B.; Eggen, M. J.; Shen, Q.; Shoemaker, R. K. *J. Org. Chem*. **1996**, *61*, 4666. (c) Martin, S. F.; Dean, D. W.; Wagman, A. S. *Tetrahedron Lett*. **1992**, *33*, 1839. (d) Lequeux, T. P.; Percy, J. M. *Synlett* **1995**, 361. (e) Benayoud, F.; Hammond, G. B. *J. Chem. Soc., Chem. Commun*. **1996** 1447. (f) Smith, M. S.; Ford, H.; Burke, T. R., Jr. *Tetrahedron Lett*. **1994**, 33, 541. (g) Qui, W.; Burton, D. J. *Tetrahedron Lett*. **1996**, *37*, 2745. (h) Taylor, S. D. Kotoris, C. C.; Dinaut, A. N.; Chen, M.-J. *Tetrahedron* **1998**, *54*, 1691. (i) Piettre, S. *Tetrahedron Lett*. **1996**, *37*, 2233. (j) Herpin, T. F.; Motherwell, W. B.; Roberts, B. P.; Roland, S.; Weibel, J.-M. *Tetrahedron* **1997**, *53*, 15085. (k)Liu, A.-R.; Chen, Q.-Y. *Synthesis* **1996**, 606. (l) Blades, K.; Percy, J. M. *Tetrahedron Lett*. **1998**, *39*, 9085.

(2) (a) Yokomatsu, T.; Suemune, K.; Murano, T.; Shibuya, S. *J. Org. Chem*. **1996**, *61*, 7207. (b) Yokomatsu, T.; Murano, T. Suemune, K.; Shibuya, S. *Tetrahedron* **1997**, *53*, 815. (c)Yokomatsu, T.; Sato, M.; Abe, H.; Suemune, K.; Matsumoto, K.; Kihara, T.; Soeda, S.; Shimeno, H.; Shibuya, S. *Tetrahedron* **1997**, *53*, 11297. (d) Yokomatsu, T.; Minowa, T.; Murano, T.; Shibuya, S. *Tetrahedron* **1998**, *54*, 9341. (e) Yokomatsu, T.; Abe, H.; Sato, M.; Suemune, K.; Kihara, T.; Soeda, S.; Shimeno, H.; Shibuya, S. *Bioorg. Med. Chem*. **1998**, *6*, 2495. (f) Yokomatsu, T.; Murano T.; Umesue, I.; Soeda, S.; Shimeno, H.; Shibuya, S. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 529.

(3) (a) Lequeux, T. P.; Percy, J. M. *J. Chem. Soc., Chem. Commun*. **1995**, 2111. (b) Blades, K.; Lequeux, T. P.; Percy, J. M. *J Chem. Soc., Chem. Commun*. **1996**, 1457.

(4) (a) Carpita, A.; Neri, D.; Rossi, R. *Gazz. Chim. Ital*. **1987**, *117*, 481. (b) Marek, I.; Alexakis, A.; Normant, J.-F. *Tetrahedron Lett*. **1991**, *32*, 5329. (c) Ma, S.; Lu, X.; Li, Z. *J. Org. Chem*. **1992**, *57*, 709. (d) Bänziger, M.; Grififths, G.; Marrity, J. F. *Tetrahedron: Asymmetry* **1993**, *4*, 723.

(5) (a) Liu, F.; Negishi, E. *J. Org. Chem*. **1997**, *62*, 8591. (b) Negishi, E.; Van Horn, D. E.; King, A. O.; Okukado, N. *Synthesis* **1979**, 501.

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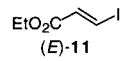
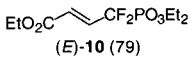
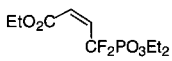
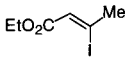
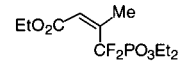
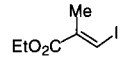
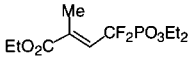
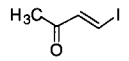
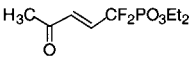
**Table 1. CuBr-Catalyzed Coupling Reaction of 1 with Iodoalkenoates and Iodoalkenones**[a]

| Entry | Substrate[b] | Product (yield%)[d] |
|---|---|---|
| 1 |  (*E*)-**11** |  (*E*)-**10** (79) |
| 2 |  (*Z*)-**11** |  (*Z*)-**10** (95) |
| 3 |  (*Z*)-**12** |  (*Z*)-**15** (70) |
| 4 |  (*E*)-**13**[c] |  (*E*)-**16** (89) |
| 5 |  (*E*)-**14** |  (*E*)-**17** (91) |

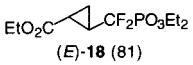
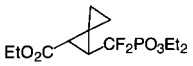
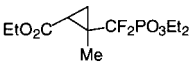
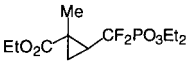
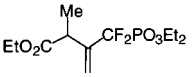
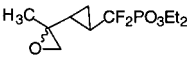
[a] All coupling reactions were carried out in DMF at 25 °C for 12 h. [b] All substrates except for (*E*)-**13** were prepared according to the literature procedures.[4] [c] Prepared from the corresponding iodoalkenol[5] as described in the supporting information. [d] Unoptimised isolated yield after purification.

When (*E*)-*β*-iodoacrylate (*E*)-**11**[4a] was treated with the zinc reagent **1** (2.0 equiv) in the presence of a stoichiometric amount of CuBr in DMF at room temperature for 12 h, the desired coupling reaction proceeded to give (*E*)-**10** in 79% isolated yield (entry 1). The (*Z*)-isomer (*Z*)-**10** was also prepared from (*Z*)-iodoacrylate (*Z*)-**11**[4b,c] in excellent yield (95%) under the same conditions (entry 2). Comparison of these coupling products on the $^1$H NMR spectra clearly revealed that the coupling reaction proceeded with complete retention of the starting geometry. Upon using the coupling reaction, (*Z*)-**15** and (*E*)-**16** of defined stereochemistry were readily prepared from 3-iodocrotonate (*Z*)-**12**[4b,c] and 3-iodomethacrylate (*E*)-**13** in reasonable yield, respectively (entries 3 and 4). (*E*)-4-Iodobut-3-en-2-one (*E*)-**14**[4d] was also a good substrate for the coupling reaction, giving (*E*)-**17** in 91% yield (entry 5); no addition product to the carbonyl was detected in this reaction.

**Preparation of Cyclopropylalkanols Possessing a Difluoromethylenephosphonate Group.** Having established an efficient method for the preparation of a series of enoates as well as an enone bearing a difluoromethylenephosphonate group, our attention was focused on the cyclopropanation reaction of these substrates with sulfur-ylides and their manipulation to a series of cyclopropylalkanols for construction of biologically interesting nucleotide analogues having a difluoromethylenephosphonic acid. The results of the cyclopropanation reaction are summarized in Table 2.

Initially, cyclopropanation reaction of enoates (*E*)-**10** and (*Z*)-**10** with representative ylides such as dimethyloxosulfonium methylide and diphenylsulfonium cyclopropylide was examined in dimethyl sulfoxide (DMSO) or dimethoxyethane (DME) according to the procedure respectively described by Corey and Trost.[6] As expected, (*E*)-**10** was rapidly (1.5 h) cyclopropanated with dimethyloxosulfonium methylide[6b] in DMSO to give the desired product (*E*)-**18** in 81% yield (entry 1). When the cyclopropanation was carried out with the corresponding *Z*-isomer (*Z*)-**10** under the same conditions, the thermodynamically more stable (*E*)-**18** was obtained as the sole product in a better yield (86%) (entry 2). Both enoates (*E*)-**10** and (*Z*)-**10** reacted with diphenylsulfonium cyclopropylide[6c] in DME to give the spiroannelation product (*E*)-**19** in moderate yield (entries 3 and 4). While the yield of (*E*)-**19** from (*Z*)-**10** appears to be slightly better than that from (*E*)-**10**, the reaction with (*Z*)-**10** accompanied the isomerization reaction giving (*E*)-**10** which was difficult to separate from the desired adduct (*E*)-**19** (entry 4).

**Table 2. Cyclopropanation of Alkenoates and Alkenones Bearing a Difluoromethylenephophonate Group with Ylides**

| Entry | Subst. | Ylide and conditions[a] | Product (yield%) |
|---|---|---|---|
| 1 | (*E*)-**10** | $CH_2$=S(O)$Me_2$[b] DMSO / 1.5 h |  (*E*)-**18** (81) |
| 2 | (*Z*)-**10** | $CH_2$=S(O)$Me_2$[b] DMSO / 1.5 h | (*E*)-**18** (86) |
| 3 | (*E*)-**10** |  [c] DME / 4 h |  (*E*)-**19** (44) |
| 4 | (*Z*)-**10** |  [c] DME / 4 h | (*E*)-**19** (50)[d] and (*E*)-**10** (14)[d] |
| 5 | (*Z*)-**15** | $CH_2$=S(O)$Me_2$[b] DMSO / 6 h |  (*E*)-**20** (56) and (*Z*)-**20** (5) |
| 6 | (*E*)-**16** | $CH_2$=S(O)$Me_2$[b] DMSO / 6 h |  (*E*)-**21** (37)[d]  **22** (5)[d] |
| 7 | (*E*)-**17** | $CH_2$=S(O)$Me_2$[b] DMSO / 6 h |  **23** (13)[e] |

[a] All reactions were carried out at 25 °C. [b] Generated from $Me_3S(O)I$ and NaH in DMSO.[6a] [c] Generated from cyclopropyldiphenylsulfonium fluoroborate and dimsylsodium in DME.[6b] [d] Yield based on $^1$H NMR (300 MHz, $CDCl_3$) analysis of an inseparable mixture of the products. [e] Unoptimized isolated yield after purification.

Examining the usefulness of the method for the synthesis of the analogous compounds, next, the cyclopropanation reaction of (*Z*)-**15** and (*E*)-**16**, having an additional methyl group at the α- or *β*-position of the carboxyester, with dimethyloxosulfonium methylide was carried out (entries 5 and 6). The reaction with (*Z*)-**15** proceeded rather slowly to give a mixture of adducts (*E*)-**20** and (*Z*)-**20** in a ratio of 12:1; these isomers were isolated in 56% and 5% yield, respectively, by column chromatography on silica gel (entry 5). The stereochemistry of (*E*)-**20** and (*Z*)-**20** was unambiguously determined on the basis of their diagnostic NOESY correlations as

(6) (a) For reviews of sulfur ylides: Trost, B. M.; Melvin, L. S., Jr. *Sulfur Ylides*; Academic Press: New York, 1975. (b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. (c) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5298.

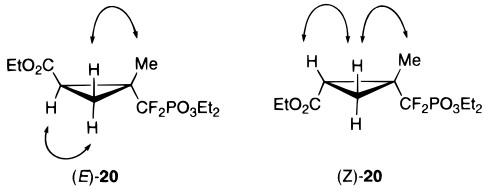



**Figure 1.** NOESY correlations of (*E*)-**20** and (*Z*)-**20**.

**Scheme 1**

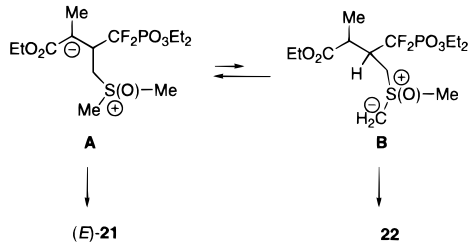



**Table 3. $LiBH_4$-Reduction of Cyclopropylcarboxylates Bearing a Difluoromethylenephosphonate Group**[a]

| Entry | Substrate | Product (yield%) |
|---|---|---|
| 1 | (*E*)-**18** | HO, $CF_2PO_3Et_2$ (*E*)-**8a** (90) |
| 2 | (*E*)-**19** | HO, $CF_2PO_3Et_2$ (*E*)-**24** (76) |
| 3 | (*E*)-**20** | HO, $CF_2PO_3Et_2$, $CH_3$ (*E*)-**25** (92) |
| 4 | (*E*)-**21**[b] | $CH_3$, HO, $CF_2PO_3Et_2$ (*E*)-**26** (34) |

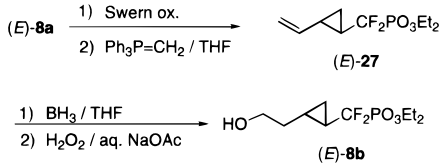
[a] All reactions were carried out in ether in the presence of a large excess of $LiBH_4$ at 25 °C. [b] A sample contaminated with **22** was used for this reaction.

shown in Figure 1. The results suggest that inversion of the configuration at the tetrahedral negative charge in the zwitterion formed initially was partially suppressed by the methyl group.[6] The reaction with (*E*)-**16** gave the desired adduct (*E*)-**21** along with the unexpected olefinic product **22**[7] in 37% and 5% yield, respectively (entry 6); the product **22** was assumed to be produced by *β-cis*-elimination reaction of the ylide **B** formed in equilibrium with the zwitterion **A** (Scheme 1).

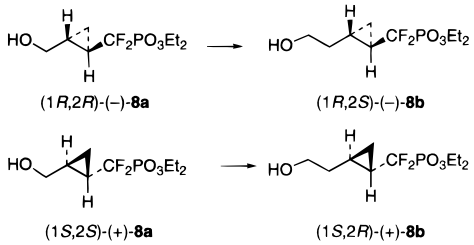
The reaction of alkenone (*E*)-**17** with dimethyloxosulfonium methylide under the same conditions gave the epoxide **23** as a mixture of diastereoisomers in a low yield (entry 7). The results suggest that competitive addition of the ylide to the carbonyl within the intermediate cyclopropane produced in the normal way is a facile process under the conditions.

The cyclopropyl carboxylate (*E*)-**18** was reduced chemoselectively with a large excess of lithium borohydride ($LiBH_4$) in ether to give the corresponding alcohol (*E*)-**8a** in 90% yield (Table 3).[8] In an analogous manner, cyclopropyl carboxylates (*E*)-**19**, (*E*)-**20**, and (*E*)-**21** were transformed to the cyclopropylmethyl alcohols (*E*)-**24**, (*E*)-**25**, and (*E*)-**26** (Table 3). The cyclopropane (*E*)-**8a** was readily transformed to the homologous alcohol (*E*)-**8b**, a

**Scheme 2**




**Scheme 3**




useful intermediate for constructing the nucleotide analogues (±)-**5b** and (±)-**6b**, by chain elongation reactions as shown in Scheme 2. Swern oxidation of (*E*)-**8a**, followed by Wittig olefination with triphenylphosphonium methylide, gave vinylcyclopropane (*E*)-**27** in 68% yield for two steps. Hydroboration of (*E*)-**27** with a borane−THF complex and subsequent oxidative workup ($H_2O_2$, aq NaOAc) provided (*E*)-**8b** in 76% yield. This sequence allowed us to synthesize optically active cyclopropanes (1*S*,2*R*)-(+)-**8b** and (1*R*,2*S*)-(−)-**8b** starting with (1*S*,2*S*)-(+)-**8a** and (1*R*,2*R*)-(−)-**8a**, which were respectively prepared by lipase-catalyzed resolution of the racemic (*E*)-**8a** as described previously (Scheme 3).[2c]

## Conclusion

In conclusion, we have conveniently prepared a series of cyclopropylalkanols bearing (diethoxyphosphory)difluoromethylene functionality at the ring, some of which were previously transformed to novel nucleotide analogues with interesting biological activities for purine nucleoside phosphorylases. The α,α-difluorophosphonate-functionalized cyclopropylalkanols prepared in this study would be useful for investigating the structure−activity relationship of nucleotide analogues related to (±)-**5b** and (±)-**6b**.

## Experimental Section

**General.** All reactions were carried out under nitrogen atmosphere. DMF was dried over molecular sieves 4 Å. DMSO was distilled from $CaH_2$. Diethyl ether and THF were freshly distilled from sodium benzophenone ketyl, respectively. DME was purchased from Aldrich and used without further purification. $^1H$ NMR spectra were recorded at 400 MHz in $CDCl_3$ using residual $CHCl_3$ (7.26 ppm) as internal references unless otherwise specified. $^{13}C$ NMR (100 MHz) and $^{31}P$ NMR (162 MHz) were taken in $CDCl_3$ using $CDCl_3$ (77.0 ppm) as an internal standard and 85% $H_3PO_4$ as an external standard, respectively, with broad-band $^1H$ decoupling. $^{19}F$ NMR spectra (376 MHz) was measured in $CDCl_3$ using benzotrifluoride (BTF) as an internal standard.

**General Experimental Procedure for CuBr-Catalyzed Reaction of 1 with Iodoacrylates and Iodoenones.** To a

(7) The structure of **22** was estimated on the basis of charactaristic signals due to the vinyl and methine protons in its $^1H$ NMR spectrum.

(8) Among various metal hydride reagents examined, $LiBH_4$ was found to be a good reducing agent for this purpose: Fieser, M. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1989; Vol. 14, p 191.

stirred suspension of zinc dust (2.4 g, 37 mmol) in dry DMF (50 mL) was slowly added a solution of **2** (9.9 g, 37 mmol) in DMF (10 mL). During the addition, exothermic reaction occurred. The addition was controlled so that the internal temperature was maintained at 50−60 °C. After addition was completed, the solution was stirred at room temperature for an additional 3 h to give the zinc reagent **1** in DMF.[2a] The solution was treated with CuBr (5.3 g, 37 mmol) at room temperature for 30 min under stirring. Iodoacrylate or iodoenone (19 mmol) in DMF (15 mL) was added dropwise at room temperature. After the mixture was stirred at room temperature for 12 h, water was added to quench the reaction. The biphasic mixture was passed through Celite and extracted with $Et_2O$. The extract was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave the crude coupling products which were purified by column chromatography on silica gel. Analytical data of (*E*)-**10**, (*Z*)-**10**, (*Z*)-**15**, (*E*)-**16**, and (*E*)-**17** obtained by this procedure are as follows:

**Ethyl (*E*)-4-(Diethoxyphosphoryl)-4,4-difluoro-2-butenoate (*E*)-10.** Obtained as an oil after column chromatography on silica gel (*n*-hexane:EtOAc = 5:1 to 3:1) in 79% yield. $^1$H NMR $\delta$ 6.95−6.84 (1H, m), 6.44−6.38 (1H, m), 4.43−4.23 (4H, m), 4.25 (2H, q, $J$ = 7.1 Hz), 1.39 (6H, t, $J$ = 7.0 Hz), 1.32 (3H, t, $J$ = 7.1 Hz); $^{13}$C NMR $\delta$ 164.1, 135.1 (dt, $J_{CP}$ = 13.1 Hz, $J_{CF}$ = 22.0 Hz), 127.8 (dt, $J_{CP}$ = 5.5 Hz, $J_{CF}$ = 9.6 Hz), 116.0 (dt, $J_{CP}$ = 217.1 Hz, $J_{CF}$ = 259.9 Hz), 64.9 (d, $J_{CP}$ = 6.7 Hz), 61.2, 16.1 (d, $J_{CP}$ = 5.1 Hz), 13.8; $^{31}$P NMR $\delta$ 5.59 (t, $J_{PF}$ = 107.7 Hz), $^{19}$F NMR $\delta$ −48.86 (2F, ddd, $J_{FP}$ = 107.7 Hz, $J_{FH}$ = 12.8, 2.3 Hz); IR (neat) 1730, 1276, 1189 cm$^{-1}$; EIMS *m*/*z* 287 ($M^+ + 1$). Anal. Calcd for $C_{10}H_{17}F_2O_5P$: C, 41.96; H, 5.99. Found: C, 41.68; H, 6.10.

**Ethyl (*Z*)-4-(Diethoxyphosphoryl)-4,4-difluoro-2-butenoate (*Z*)-10.** Obtained as an oil after column chromatography on silica gel (*n*-hexane:EtOAc = 5:1 to 3:1) in 95% yield. $^1$H NMR $\delta$ 6.28−6.24 (1H, m), 6.04−5.93 (1H, m), 4.35−4.24 (4H, m), 4.24 (2H, q, $J$ = 7.1 Hz), 1.39 (6H, t, $J$ = 7.1 Hz), 1.31 (3H, t, $J$ = 7.1 Hz); $^{13}$C NMR $\delta$ 164.6, 128.5−128.3 (m), 127.2 (dt, $J_{CP}$ = 14.1 Hz, $J_{CF}$ = 22.0 Hz), 116.1 (dt, $J_{CP}$ = 216.5 Hz, $J_{CF}$ = 261.1 Hz), 64.9 (d, $J_{CP}$ = 6.5 Hz), 61.1, 16.2 (d, $J_{CP}$ = 4.8 Hz), 13.8; $^{31}$P NMR $\delta$ 5.69 (t, $J_{PF}$ = 106.7 Hz); $^{19}$F NMR $\delta$ −45.24 (2F, ddd, $J_{FP}$ = 106.7 Hz, $J_{FH}$ = 15.4, 2.6 Hz); IR (neat) 1739, 1275, 1150 cm$^{-1}$; EIMS *m*/*z* 287 ($M^+ + 1$). Anal. Calcd for $C_{10}H_{17}F_2O_5P$: C, 41.96; H, 5.99. Found: C, 41.59; H, 6.17.

**Ethyl (*Z*)-4-(Diethoxyphosphoryl)-4,4-difluoro-3-methyl-2-butenoate (*Z*)-15.** Obtained as an oil after column chromatography on silica gel (*n*-hexane:EtOAc = 9:1) in 70% yield. $^1$H NMR $\delta$ 6.05−6.03 (1H, m), 4.36−4.25 (4H, m), 4.20 (2H, q, $J$ = 7.1 Hz), 2.04 (3H, t, $J_{HF}$ = 1.7 Hz), 1.39 (6H, t with small splits, $J$ = 7.1 Hz), 1.29 (3H, t, $J$ = 7.1 Hz); $^{13}$C NMR $\delta$ 165.1, 136.4 (dt, $J_{CP}$ = 13.6 Hz, $J_{CF}$ = 19.8 Hz), 124.6−124.4 (m) 117.9 (dt, $J_{CP}$ = 212.3 Hz, $J_{CF}$ = 263.9 Hz), 64.8 (d, $J_{CP}$ = 6.8 Hz), 60.8, 18.9 (s with small splits), 16.2 (d, $J_{CP}$ = 5.5 Hz), 13.8; $^{31}$P NMR $\delta$ 5.59 (t, $J_{PF}$ = 108.8 Hz), $^{19}$F NMR $\delta$ −44.79 (2F, d, $J_{FP}$ = 108.8 Hz); IR (neat) 1736, 1274 cm$^{-1}$; EIMS *m*/*z* 300 ($M^+$). Anal. Calcd for $C_{11}H_{19}F_2O_5P$: C, 44.00; H, 6.38. Found: C, 43.60; H, 6.25.

**Ethyl (*E*)-4-(Diethoxyphosphoryl)-4,4-difluoro-2-methyl-2-butenoate (*E*)-16.** Obtained as an oil after column chromatography on silica gel (*n*-hexane:EtOAc = 3:1) in 89% yield. $^1$H NMR $\delta$ 6.67 (1H, t, $J_{HF}$ = 15.9 Hz), 4.33−4.21 (6H, m), 2.10 (3H, s), 1.38 (6H, t, $J$ = 7.1 Hz), 1.31 (3H, t, $J$ = 7.1 Hz); $^{13}$C NMR $\delta$ 166.3, 138.3 (dt, $J_{CP}$ = 6.4 Hz, $J_{CF}$ = 6.4 Hz), 128.5 (dt, $J_{CP}$ = 12.7 Hz, $J_{CF}$ = 22.8 Hz), 117.4 (dt, $J_{CP}$ = 217.8 Hz, $J_{CF}$ = 259.7 Hz), 64.7 (d, $J_{CP}$ = 6.8 Hz), 61.4, 16.2 (d, $J_{CP}$ = 5.4 Hz), 13.9, 13.6; $^{31}$P NMR $\delta$ 6.28 (t, $J_{PF}$ = 110.3 Hz); $^{19}$F NMR $\delta$ −43.94 (1F, ddd, $J_{HF}$ = 3.0, 15.9 Hz, $J_{FP}$ = 110.3 Hz); IR (neat) 1723, 1268 cm$^{-1}$; EIMS *m*/*z* 301 ($M^+ + 1$). Anal. Calcd for $C_{11}H_{19}F_2O_5P$: C, 44.00; H, 6.38. Found: C, 43.85; H, 6.40.

**(*E*)-5-(Diethoxyphosphoryl)-5,5-difluoropent-3-en-2-one (*E*)-17.** Obtained as an oil after column chromatography on silica gel (*n*-hexane:EtOAc = 2:1) in 91% yield. $^1$H NMR $\delta$ 6.75−6.56 (2H, m), 4.35−4.22 (2H, m), 2.35 (3H, s), 1.38 (3H, t, $J$ = 7.1 Hz); $^{13}$C NMR $\delta$ 196.2, 134.5 (d, $J_{CP}$ = 5.3 Hz), 133.3 (dt, $J_{CP}$ = 13.0 Hz, $J_{CF}$ = 22.0 Hz), 116.3 (dt, $J_{CP}$ = 216.0 Hz, $J_{CF}$ = 260.0 Hz), 65.0 (d, $J_{PC}$ = 6.5 Hz), 28.0, 16.3 (d, $J_{CP}$ = 5.0 Hz); $^{31}$P NMR $\delta$ 6.22 (t, $J_{PF}$ = 107.4 Hz), $^{19}$F NMR $\delta$ −48.33 (1F, dd, $J_{FH}$ = 11.5 Hz, $J_{FP}$ = 107.4 Hz); IR (neat) 1690, 1271 cm$^{-1}$; EIMS *m*/*z* 257 ($M^+$). Anal. Calcd for $C_9H_{15}F_2O_4P$: C, 42.19; H, 5.90. Found: C, 42.10; H, 6.09.

**Representative Procedure for Cyclopropanation of Alkenoates with Dimethyloxosulfonium Methylide (Synthesis of Ethyl (1*R**,2*R**)-2-[(Diethoxyphosphoryl)(difluoro)methyl]cyclopropane-1-carboxylate (*E*)-18 from (*Z*)-10).** To a mixture of sodium hydride (475.3 mg, prewashed with *n*-hexane) and trimethyloxosulfonium iodide (2.61 g, 11.9 mmol) was added DMSO (50 mL) at room temperature. Vigorous gas evolution was observed. The mixture was stirred at room temperature for 30 min. A solution of (*Z*)-**10** (3.09 g, 10. 8 mmol) in DMSO (50 mL) was dropwise added at room temperature. After being stirred for 1.5 h, the mixture was poured onto cold ice−water. The biphasic mixture was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and evaporated to give almost pure (*E*)-**18** (2.85 g, 88%) as an oil: $^1$H NMR $\delta$ 4.32−4.24 (4H, m), 4.16 (2H, q, $J$ = 7.1 Hz), 2.17−2.01 (2H, m), 1.39 (6H, t with small splits, $J$ = 7.1 Hz), 1.36−1.23 (2H, m), 1.27 (3H, t, $J$ = 7.1 Hz); $^{13}$C NMR $\delta$ 171.7, 117.4 (dt, $J_{CP}$= 222.2 Hz, $J_{CF}$ = 260.3 Hz), 64.4 (d with small splits, $J_{CP}$ = 4.7 Hz), 60.9, 22.4 (dt, $J_{CP}$ = 19.7 Hz, $J_{CF}$ = 24.4 Hz), 16.2 (d, $J_{CP}$ = 5.2 Hz), 13.9, 10.1 (s with small splits); $^{31}$P NMR $\delta$ 6.84 (t, $J_{PF}$ = 112.7 Hz); $^{19}$F NMR $\delta$ −50.25 (1F, ddd, $J_{FF}$ = 297.8 Hz, $J_{FP}$ = 112.7 Hz, $J_{FH}$ = 11.7 Hz), −54.32 (1F, ddd, $J_{FF}$ = 298.1 Hz, $J_{FP}$ = 112.7 Hz), $J_{FH}$ = 15.1 Hz); IR (neat) 1732, 1275, 1189 cm$^{-1}$; EIMS *m*/*z* 300 ($M^+$). Anal. Calcd for $C_{11}H_{19}F_2O_5P$: C, 44.00; H, 6.38. Found: C, 43.96; H, 6.53.

**Ethyl (1*S**,2*S**)-2-[(Diethoxyphosphoryl)(difluoro)methyl]spiro [2,2]pentane-1-carboxylate (*E*)-19.** To a stirred suspension of cyclopropyldiphenylsulfonium fluoroborate (343 mg, 1.1 mmol) in DME (10 mL) was added dimsylsodium (1.2 mL of 1.06 M solution in DMSO, 1.3 mmol) at −40 °C. After the reaction was stirred at the same temperature for 30 min, a solution of (*E*)-**10** (312 mg, 1.1 mmol) in DME (5 mL) was added. The mixture was stirred at −40 °C for 15 min and gradually warmed to room temperature during 1 h. The reaction was quenched by addition of water. The mixture was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (*n*-hexane:EtOAc = 5:1) to give (*E*)-**19** (155 mg, 44%) as an oil: $^1$H NMR $\delta$ 4.36−4.20 (4H, m), 2.53−2.40 (1H, m), 2.36 (1H, d, $J$ = 3.8 Hz), 1.42−1.35 (1H, m), 1.37 (6H, t, $J$ = 7.0 Hz), 1.29−1.20 (1H, m), 1.26 (3H, t, $J$ = 7.1 Hz), 1.10−1.02 (1H, m), 0.94−0.88 (1H, m); $^{13}$C NMR $\delta$ 171.1, 117.7 (dt, $J_{CP}$ = 221.6 Hz, $J_{CF}$ = 260.6 Hz), 64.2 (d with small splits, $J_{CP}$ = 7.5 Hz), 60.5, 27.2 (dt, $J_{CP}$ = 20.4 Hz, $J_{CF}$ = 23.4 Hz), 22.5 (s with small splits), 20.2 (d, $J_{CP}$ = 8.0 Hz), 16.2 (d, $J_{CP}$ = 4.6 Hz), 14.0, 5.3, 4.5; $^{31}$P NMR $\delta$ 6.96 (t, $J_{PF}$ = 112.9 Hz); $^{19}$F NMR $\delta$ −47.87 (1F, ddd, $J_{FF}$ = 299.7 Hz, $J_{FP}$ = 112.9 Hz, $J_{FH}$ = 11.3 Hz), −54.24 (1F, ddd, $J_{FF}$ = 299.7 Hz, $J_{FP}$ = 112.9 Hz, $J_{FH}$ = 11.3 Hz); IR (neat) 1734, 1274, 1186 cm$^{-1}$; EIMS *m*/*z* 327 ($M^+ + 1$), 326 ($M^+$). High-resolution MS (EI) *m*/*z* calcd for $C_{13}H_{21}F_2O_5P$ ($M^+$): 326.1095. Observed: 326.1095.

**Ethyl (1*R**,2*R**)-2-[(Diethoxyphosphoryl)(difluoro)methyl]-2-methylcyclopropane-1-carboxylate (*E*)-20 and Ethyl (1*S**,2*R**)-2-[(Diethoxyphosphoryl)(difluoro)methyl]-2-methylcyclopropane-1-carboxylate (*Z*)-20.** The alkenoate (*Z*)-**15** (1.71 g, 5.7 mmol) was treated with dimethyloxosulfonium methylide, generated from trimethyloxosulfonium iodide (2.13 g, 9.7 mmol) and sodium hydride (388 mg, 9.7 mmol), in DMSO (75 mL) for 6 h in an analogous manner to that for the preparation of (*E*)-**18**. Column chromatography of the crude materials on silica gel eluted with *n*-hexane:EtOAc = 9:1 gave (*E*)-**20** (997 mg, 56%) as an oil: $^1$H NMR $\delta$ 4.33−4.23 (4H, m) 4.23−4.11 (2H, m), 2.14 (1H, dd, $J$ = 6.4, 8.9 Hz), 1.44 (3H, s), 1.41−1.37 (1H, m), 1.40 (3H, t, $J$ = 7.1 Hz), 1.39 (3H, t, $J$ = 7.1 Hz), 1.28 (3H, t, $J$ = 7.1 Hz), 1.20−1.17 (1H, m); $^{13}$C NMR $\delta$ 170.6, 119.1 (dt, $J_{CP}$ = 218.3 Hz, $J_{CF}$ = 263.7 Hz), 64.3 (d, $J_{CP}$ = 7.2 Hz), 64.2 (d, $J_{CP}$ = 7.2 Hz), 60.7, 27.3 (dt, $J_{CP}$ = 20.0 Hz, $J_{CF}$ = 22.3 Hz), 21.8 (d, $J_{CP}$ = 2.4 Hz), 16.2 ($J_{CP}$ = 5.4 Hz), 15.7, 14.1, 12.2; $^{31}$P NMR $\delta$ 6.88 (t, $J_{PF}$ = 114.9 Hz), $^{19}$F NMR $\delta$ −52.48 (2F, dd, $J_{FP}$ = 114.9 Hz, $J_{FH}$ = 5.6 Hz); IR (neat) 1731, 1275, 1189 cm$^{-1}$; EIMS *m*/*z* 314 ($M^+$). Anal. Calcd for $C_{12}H_{21}F_2O_5P$: C, 45.86, H, 6.74. Found: C, 45.79; H, 6.72. Further elution with *n*-hexane:EtOAc = 8:1 gave (*Z*)-**20** (90 mg, 5%) as an oil: $^1$H NMR $\delta$ 4.33−4.21 (4H, m), 4.20−4.12 (2H, m), 1.76−1.68 (2H, m), 1.42 (3H, s), 1.38 (6H, t, $J$ = 7.1 Hz), 1.26 (3H, m), 1.01−0.97 (1H, m), $^{31}$P NMR $\delta$ 6.56 (t, $J_{PF}$ = 114.0 Hz); $^{19}$F NMR $\delta$ −47.83 (2F, dd, $J_{FP}$ = 114.0 Hz, $J_{FH}$ = 10.2 Hz); IR (neat) 1738,

1273, 1191 $cm^{-1}$; EIMS *m/z* 314 ($M^+$). Anal. Calcd for $C_{12}H_{21}F_2O_5P$: C, 45.86, H, 6.74. Found: C, 45.94; H, 6.77.

**Cyclopropanation of (*E*)-16 with Dimethylsulfonium Methylide. (For Preparation of Ethyl (1*R**,2*S**)-2-[(Diethoxyphosphoryl)(difluoro)methyl]-1-methylcyclopropane-1-carboxylate (*E*)-21).** Alkenoate (*E*)-**16** (600 mg, 2.0 mmol) was treated with dimethyloxosulfonium methylide, generated from trimethyloxosulfonium iodide (748 mg, 3.4 mmol) and sodium hydride (136 mg, 3.4 mmol), in DMSO (15 mL) for 6 h in an analogous manner to that for the preparation of (*E*)-**18**. The crude was chromatographed on silica gel (*n*-hexane: EtOAc = 3:1) to give (*E*)-**21** (260 mg, 42%) contaminated with a small amount (5%) of the olefinic product **22** [$^1$H NMR $\delta$ 5.83 (dt, $J$ = 2.3, 2.3 Hz), 5.64 (d, $J$ = 1.6 Hz), 3.51 (q, $J$ = 6.6 Hz), 1.36 (d, $J$ = 6.6 Hz), EIMS *m/z* 315 ($M^+ + 1$)]. Analytical samples for (*E*)-**21** was obtained by preparative TLC (*n*-hexane:EtOAc = 1:1, Merck 5744, 20 cm × 10 cm). Spectroscopic data of (*E*)-**21** are as follows: an oil; $^1$H NMR $\delta$ 4.32−4.25 (4H, m), 4.13 (2H, q, $J$ = 7.1 Hz), 2.24−2.10 (1H, m), 1.56−1.51 (1H, m), 1.49 (3H, s), 1.39 (6H, t, $J$ = 6.8 Hz), 1.25 (3H, t, $J$ = 7.1 Hz), 1.12−1.09 (1H, m); $^{13}$C NMR $\delta$ 173.5, 119.2 (dt, $J_{CP}$ = 221.1 Hz, $J_{CF}$ = 260.9 Hz), 64.5 (d, $J_{CP}$ = 3.9 Hz), 64.4 (d, $J_{CP}$ = 6.1 Hz), 61.2, 26.3 (dt, $J_{CP}$ = 21.9 Hz, $J_{CF}$ = 21.9 Hz), 24.2 (d, $J_{CP}$ = 5.2 Hz), 18.3, 16.3 (d, $J_{CP}$ = 2.9 Hz), 14.0, 13.7. $^{31}$P NMR $\delta$ 6.59 (t, $J_{PF}$ = 112.2 Hz); $^{19}$F NMR $\delta$ −46.17 (1F, ddd, $J_{FH}$ = 9.0 Hz, $J_{FP}$ = 112.2 Hz, $J_{FF}$ = 299.3 Hz), −48.35 (1F, ddd, $J_{FH}$ = 22.1 Hz, $J_{FP}$ = 112.2 Hz, $J_{FF}$ = 299.3 Hz). IR (neat) 1726, 1274 $cm^{-1}$; EIMS *m/z* 315 ($M^+ + 1$). Anal. Calcd for $C_{12}H_{21}F_2O_5P$: C, 45.86; H, 6.74. Found: C, 45.60; H, 6.77.

**Reaction of Alkenone (*E*)-17 with Dimethyloxosulfonium Methylide in DMSO.** Alkenone (*E*)-**17** (641 mg, 2.5 mmol) was treated with dimethyloxosulfounium methylide, generated from trimethyloxosulfonium iodide (935 mg, 4.3 mmol) and sodium hydride (170 mg, 4.3 mmol), in DMSO (15 mL) in an analogous manner to that for preparation of (*E*)-**18**. The crude was purified by column chromatography on silica gel (*n*-hexane: EtOAc = 2:1) to give **23** (92 mg, 13%) as an oil: $^1$H NMR $\delta$ 4.32−4.23 (4H, m), 2.67−2.57 (2H, m), 1.60−1.50 (1H, m), 1.42−1.39 (3H, m), 1.38 (6H, t, $J$ = 7.0 Hz), 1.00−0.83 (1H, m), 0.81−0.63 (2H, m); $^{31}$P NMR $\delta$ 8.27 (0.42P, t, $J_{PF}$ = 116.8 Hz), 8.16 (0.58P, t, $J_{PF}$ = 116.6 Hz); IR (neat) 1272 $cm^{-1}$; EIMS *m/z* 285 ($M^+ + 1$). High-resolution MS (EI) *m/z* calcd for $C_{11}H_{20}F_2O_4P$ ($MH^+$): 285.1067. Observed: 285.1047.

**Diethyl Difluoro[(1*R**,2*R**)-2-(hydroxymethyl)cyclopropyl] methylphosphonate (*E*)-8a.** To a stirred solution of (*E*)-**18** (4.5 g, 15 mmol) in ether (20 mL) was added $LiBH_4$ (5.6 mg, 15 mmol) in one portion at room temperature. After being stirred for 1 h, the reaction was quenched by addition of water. The mixture was extracted with chloroform, and the organic extracts were washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave (*E*)-**8a** (4.06 g, 90%). The spectroscopic data of (*E*)-**8a** was identical to those of an authentic sample prepared previously.[2c]

**Diethyl Difluoro[(1*S**,2*S**)-2-hydroxymethyl)spiro[2,2]-pent-1-yl]methylphosphophonate (*E*)-24.** The ester (*E*)-**19** (241 mg, 0.7 mmol) was reduced with $LiBH_4$ (77 mg, 3.5 mmol) in ether (5 mL) for 2 h. Workup as above, followed by chromatography on silica gel (*n*-hexane:EtOAc = 2:1), gave (*E*)-**24** (147 mg, 76%) as an oil. $^1$H NMR $\delta$ 4.33−4.24 (4H, m), 3.86−3.76 (1H, m), 3.47−3.43 (1H, m), 1.88−1.83 (1H, m), 1.72−1.64 (1H, m), 1.39 (1H, t, $J$ = 7.1 Hz), 1.13−1.08 (1H, m), 0.96−0.92 (1H, m), 0.86−0.80 (1H, m); $^{13}$C NMR $\delta$ 119.2 (dt, $J_{CP}$ = 221.1 Hz, $J_{CF}$ = 259.9 Hz), 64.4 (d with small splits, $J_{CP}$ = 6.2 Hz), 63.7, 24.1 (dt, $J_{CP}$ = 19.4 Hz, $J_{CF}$ = 23.7 Hz), 23.0 (t, $J_{CF}$ = 2.8 Hz), 3.9, 2.7; $^{31}$P NMR (162 MHz, $CDCl_3$) $\delta$ 8.11 (t, $J_{PF}$ = 115.0 Hz); $^{19}$F NMR $\delta$ −48.46 (1F, ddd, $J_{FF}$ = 296.3 Hz, $J_{FP}$ = 115.0 Hz, $J_{FH}$ = 8.7 Hz), −53.51 (1F, ddd, $J_{FF}$ = 296.3 Hz, $J_{FP}$ = 115.0 Hz, $J_{FH}$ = 18.8 Hz); IR (neat) 3442, 1264 $cm^{-1}$. EIMS *m/z* 284 ($M^+$); High-resolution MS (EI) *m/z* calcd for $C_{11}H_{19}F_2O_4P$ ($M^+$): 284.0989. Observed: 284.1004.

**Diethyl Difluoro[(1*R**,2*R**)-2-(hydroxymethyl)-1-methylcyclopropyl]methylphosphonate (*E*)-25.** The ester (*E*)-**20** (272 mg, 0.9 mmol) was reduced with $LiBH_4$ (98 mg, 4.5 mmol) in ether (5 mL) for 4.5 h. Workup as above, followed by chromatography on silica gel (*n*-hexane:EtOAc = 3:1), gave (*E*)-**25** (216 mg, 92%) as an oil. $^1$H NMR $\delta$ 4.32−4.20 (4H, m), 3.96−3.91 (1H, m), 1.82 (1H, broad s), 1.55−1.47 (1H, m), 1.40 (3H, t, $J$ = 7.0 Hz), 1.38 (3H, t, $J$ = 6.9 Hz), 1.37 (3H, s), 1.31−1.25 (1H, m), 0.41−0.38 (1H, m); $^{13}$C NMR $\delta$ 120.2 (dt with small splits, $J_{CP}$ = 216.6 Hz, $J_{CF}$ = 266.2 Hz), 64.4 (d, $J_{CP}$ = 6.6 Hz), 64.2 (d, $J_{CP}$ = 7.2 Hz), 61.2, 22.7−22.1 (m), 21.8 (s with small splits), 16.2 (d, $J_{CP}$ = 5.4 Hz), 13.8 (s with small splits), 12.8; $^{31}$P NMR $\delta$ 8.31 (dd, $J_{PF}$ = 114.0, 119.5 Hz); $^{19}$F NMR $\delta$ −50.10 (1F, dd, $J_{FF}$ = 291.4 Hz, $J_{FP}$ = 114.0 Hz), −55.65 (1F, dd, $J_{FF}$ = 291.4 Hz, $J_{FP}$ =119.5 Hz); IR (neat) 3447, 1262, 1038 $cm^{-1}$; EIMS *m/z* 273 ($M^+ + 1$). Anal. Calcd for $C_{10}H_{19}F_2O_4P$: C, 44.12, H, 7.04. Found: C, 44.32; H, 7.07.

**Diethyl Difluoro[(1*R**,2*R**)-2-(hydroxymethyl)-2-methylcyclopropyl]methylphosphonate (*E*)-26.** The ester (*E*)-**21** (154 mg, 0.49 mmol) was reduced with $LiBH_4$ (74 mg, 3.4 mmol) for 2.0 h in ether (3 mL) in an analogous manner to that for the preparation of (*E*)-**8a**. Workup as above, followed by column chromatography on silica gel (*n*-hexane: EtOAc = 1:1 to EtOAc), gave (*E*)-**26** (92 mg, 34%). $^1$H NMR $\delta$ 4.32−4.25 (4H, m), 3.52 (1H, d, $J$ = 10.9 Hz), 3.29 (1H, d, $J$ = 10.9 Hz), 1.49−1.35 (1H, m), 1.39 (3H, t, $J$ = 7.1 Hz), 1.33 (3H, s), 0.93−0.87; $^{13}$C NMR $\delta$ 120.3 (dt, $J_{CP}$ = 221.3 Hz, $J_{CF}$ = 260.3 Hz), 69.8, 64.5 (d, $J_{CP}$ = 5.8 Hz), 64.4 (d, $J_{CP}$ = 5.2 Hz), 24.3 (d, $J_{CP}$ = 3.1 Hz), 22.4 (dt, $J_{CP}$ = 21.9 Hz, $J_{CF}$ = 21.9 Hz), 16.33 (d, $J_{CP}$ = 5.1 Hz), 16.28 (d, $J_{CP}$ = 5.1 Hz), 14.9 (d, $J_{CP}$ = 3.2 Hz), 13.3; $^{31}$P NMR $\delta$ 8.51 (t, $J_{PF}$ = 115.4 Hz); $^{19}$F NMR $\delta$ −43.88 (1F, ddd, $J_{FH}$ = 18.8 Hz, $J_{FP}$ = 115.4 Hz, $J_{FF}$ = 297.2 Hz), −47.46 (1F, ddd, $J_{FH}$ = 15.0 Hz, $J_{FP}$ = 115.4 Hz, $J_{FF}$ = 297.2 Hz); IR (neat) 3433, 1258 $cm^{-1}$; EIMS *m/z* 273 ($M^+ + 1$). Anal. Calcd for $C_{10}H_{19}F_2O_4P$:C,44.12; H, 7.04. Found: C, 43.91; H, 7.19.

**Diethyl Difluoro[(1*R**,2*S**)-2-vinylcyclopropyl]methylphosphonate (*E*)-27.** The Swern reagent in $CH_2Cl_2$ (60 mL) was prepared from oxaryl chloride (0.97 mL, 11 mmol) and DMSO (1.59 mL, 22 mmol) at −78 °C.[9] To this solution was added a solution of (*E*)-**8a** (2.41 g, 9.3 mmol) in $CH_2Cl_2$ (25 mL) at the same temperature. After the reaction was stirred for 30 min, triethylamine (6.5 mL, 47 mmol) was added. The mixture was stirred at 0 °C for 20 min and gradually warmed to room temperature for 30 min. Workup as usual gave the crude aldehyde as an oil: $^1$H NMR $\delta$ 9.40 (1H, d, $J$ = 3.9 Hz), 4.33−4.24 (4H, m), 2.37−2.30 (1H, m), 2.25−2.12 (1H, m), 1.46−1.37 (2H, m), 1.40 (6H, t, $J$ = 7.2 Hz). This oil was used for the next reaction without purification. To a stirred solution of triphenylphosphonium methylide in THF (65 mL), generated from methyltriphenyphosphonium iodide (6.38 g, 18 mmol) and *n*-butyllithium (11.3 mL of 1.6 M hexane solution, 18 mmol), was added a solution of the crude aldehyde (2.28 g, 8.9 mmol) in THF (25 mL) under ice-cooling. After being stirred for 30 min at room temparature, the mixture was poured on sat. $NH_4Cl$. The biphasic mixture was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 9:1 to 7:1) to give (*E*)-**27** (1.62 g, 68% from (*E*)-**8**). $^1$H NMR $\delta$ 5.49−5.40 (1H, m), 5.16 (1H, d, $J$ = 16.9 Hz), 4.99 (1H, d, $J$ = 10.2 Hz), 4.32−4.23 (4H, m), 1.88−1.82 (1H, m), 1.55−1.45 (1H, m), 1.38 (6H, t, $J$ = 7.1 Hz), 1.19−1.14 (1H, m), 0.86−0.81 (1H, m); $^{13}$C NMR $\delta$ 137.9, 118.9 (dt, $J_{CP}$ = 222.8 Hz), $J_{CF}$ = 259.4 Hz), 114.6, 64.3 (d, $J_{CP}$ = 7.0 Hz), 21.5 (dt, $J_{CP}$ = 19.6 Hz, $J_{CF}$ = 23.8 Hz), 18.5, 16.4 (d, $J_{CP}$ = 5.5 Hz), 9.3; $^{31}$P NMR $\delta$ 7.55 (t, $J_{PF}$ = 115.2 Hz); $^{19}$F NMR $\delta$ −51.71 (2F, dd, $J_{FP}$ = 115.2 Hz, $J_{FH}$ = 13.7 Hz); IR (neat) 1642, 1272 $cm^{-1}$; EIMS *m/z* 254 ($M^+$). Anal. Calcd for $C_{10}H_{17}F_2O_3P$: C, 47.24; H, 6.74. Found: C, 47.16; H, 6.94.

**Diethyl Difluoro[(1*S*,2*R*)-2-vinylcyclopropyl]methylphosphonate (1*S*,2*R*)-27.** Optically active alcohol (1*S*,2*S*)-**8a** (>95% ee, $[\alpha]^{25}_D$ +29.4 (*c* 1.04, MeOH)), prepared from (*E*)-**8a** by the enzymatic resolution as described previously,[2c] was transformed to (1*S*,2*R*)-**27** (an oil) in an analogous manner to that for preparation of (*E*)-**27**. The spectroscopic data of (1*S*,2*R*)-**27** was identical to those of (*E*)-**27** except for the specific rotation: $[\alpha]^{25}_D$ +25.98 (*c* 1.02, MeOH).

**Diethyl Difluoro[(1*R*,2*S*)-2-vinylcyclopropyl]methylphosphonate (1*R*,2*S*)-27.** Optically active alcohol (1*R*,2*R*)-**8a** (>95% *ee*, $[\alpha]^{25}_D$ −29.6 (*c* 1.12, MeOH)), prepared from (*E*)-**8a** by the enzymatic resolution as described previously,[2c] was transformed

(9) Mancuso, A. I.; Huang, S.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

to (1*R*,2*S*)-**27** (an oil) in an analogous manner to that for preparation of (*E*)-**27**. The spectroscopic data of (1*R*,2*S*)-**27** was identical to those of (*E*)-**27** except for the specific rotation: $[\alpha]^{25}_{D}$ +21.68 (*c* 1.02, MeOH).

**Diethyl Difluoro[(1*R**,2*S**)-2-(2-hydroxyethyl)cyclopropyl]methylphosphonate (*E*)-8b.** To a stirred solution of (*E*)-**27** (1.54 g, 6.1 mmol) in THF (16 mL) was added a THF solution of a borane−tetrahydrofuran complex (1.0 M solution, 6.1 mL, 6.1 mmol) under ice-cooling. The mixture was stirred at room temperature for 3 h. Hydrogen peroxide (30%, 4.1 mL) and 3 N sodium acetate (2.0 mL) were successively added. The mixture was stirred at room temperature for 1 h. The biphasic mixture was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 5:1) to give (*E*)-**8b** (1.26 g, 76%) as an oil. The spectroscopic data of (*E*)-**8b** was identical to those of an authentic sample prepared previously.[2e]

**Diethyl Difluoro[(1*S*,2*R*)-2-(2-hydroxyethyl)cyclopropyl]methylphosphonate (1*S*,2*R*)-8b.** This compound was prepared from (1*S*,2*R*)-**27** in an analogous manner to that for preparation of (*E*)-**8b**. The spectroscopic data of (1*S*,2*R*)-**8b** was identical to those of (*E*)-**8b** except for the specific rotation: $[\alpha]^{25}_{D}$ +20.92 (*c* 1.04, MeOH).

**Diethyl Difluoro[(1*R*,2*S*)-2-(2-hydroxyethyl)cyclopropyl]methylphosphonate (1*R*,2*S*)-8b.** This compound was prepared from (1*R*,2*S*)-**27** in an analogous manner to that for preparation of (*E*)-**8b**. The spectroscopic data of (1*R*,2*S*)-**8b** was identical to those of (*E*)-**8b** except for the specific rotation: $[\alpha]^{25}_{D}$ −20.49 (*c* 1.04, MeOH).

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**Supporting Information Available:** Experimental procedure for preparation of (*E*)-**13**. This material is avilable free of charge via the Internet at http://pubs.acs.org.

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