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Tandem reduction–olefination of triethyl 2-acyl-2-fluoro-2-phosphonoacetates and a synthetic approach to Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly dipeptide isostere

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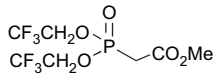
Abstract—(*Z*)-α-Fluoro-α,β-unsaturated esters (*Z*)-**7a–f** were stereoselectively prepared by a tandem reduction–olefination of triethyl 2-acyl-2-fluoro-2-phosphonoacetates **6a–f** with $NaBH_4$ in EtOH. A concise synthesis of Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly (**26**) as a dipeptide isostere was achieved via the tandem reduction–olefination of the corresponding 2-acyl-2-fluoro-2-phosphonoacetate **20**.

1. Introduction

There is currently much interest in the synthesis of α-fluoro-α,β-unsaturated carbonyl compounds as valuable building blocks for biologically active compounds.[1–6] Recent efforts in our laboratory have focused on the stereoselective Horner–Wadsworth–Emmons (HWE) reactions for the synthesis of α,β-unsaturated esters or α,β-unsaturated carboxylic acids using HWE reagents,[7–17] such as methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (**1**),[18] bis-(2,2,2-trifluoroethyl)phosphonoacetic acid (**2**),[15,19] triethyl 2-fluoro-2-phosphonoacetate (**3**),[20] and 2-fluoro-2-diethylphosphonoacetic acid (**4**).[3] Although, the stereoselective synthesis of (*E*)-α-fluoro-α,β-unsaturated esters utilizing the HWE reaction of phosphonoacetate **3** with aldehydes is well known,[21–32] there are few reports on the stereoselective HWE reaction, which was successfully employed in the synthesis of (*Z*)-α-fluoro-α,β-unsaturated esters.



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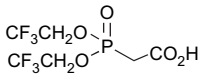

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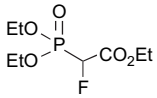

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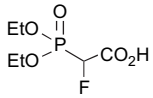

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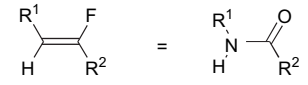
We have demonstrated the HWE reaction of various aldehydes with 2-fluoro-2-diethylphosphonoacetic acid (**4**) with *i*-PrMgBr in THF.[13] However, the HWE reactions resulted in satisfactory *Z*-selectivities only for aromatic and α,β-unsaturated aldehydes. Consequently, we describe herein a tandem reduction–olefination of triethyl 2-acyl-2-fluoro-2-phosphonoacetates **6a–f** for the stereoselective synthesis of (*Z*)-α-fluoro-α,β-unsaturated esters (*Z*)-**7a–f**.[33] In addition, to expand the application of this methodology, we achieved a concise synthesis of Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly (**26**) as a dipeptide isostere based on the tandem reduction–olefination. It is well known that fluoroolefins play an important role as amide isosteres, from the standpoint of mimicking of the steric demand, bond lengths, and bond angles.[34–49] Namely, (*Z*)-fluoroolefins mimic the (s-*Z*)-amide bonds, as shown in Figure 1.



(*Z*)-fluoroolefin (s-*Z*)-amide

Figure 1. (*Z*)-Fluoroolefins mimic the (s-*Z*)-amide bonds.

2. Results and discussion

2.1. Tandem reduction–olefination of triethyl 2-acyl-2-fluoro-2-phosphonoacetate

Triethyl 2-acyl-2-fluoro-2-phosphonoacetates **6a–f** were prepared by the treatment of commercially available triethyl 2-fluoro-2-phosphonoacetate (**3**) with *n*-BuLi (1.05 mol equiv) in THF at 0 °C, followed by acylation of the resulting

Keywords: Reduction; Olefination; Fluorine; Phosphonoacetates; α-Fluoro-α,β-unsaturated esters; Dipeptide isosteres.
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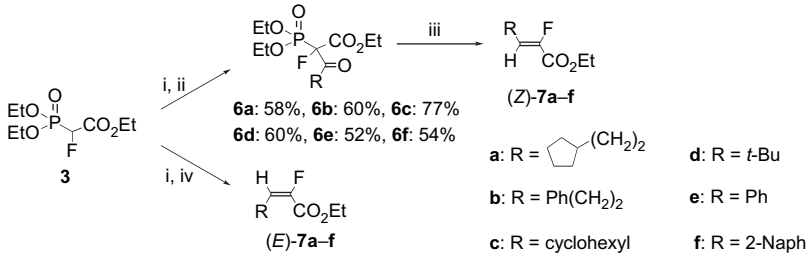


Scheme 1. Reagents and conditions: (i) *n*-BuLi, THF, 0 °C, 1 h; (ii) RCOCl **5a–f**, THF, 0 °C, **a**: 2 h, **b**: 1 h, **c**: 5 h, **d**: 6 h, **e**: 1 h, **f**: 1 h; (iii) $NaBH_4$, EtOH, −78 °C to rt (Table 1); (iv) RCHO **8a–f**, THF, rt (Table 2).

lithium enolate with acyl chlorides **5a–f** (1.05 mol equiv) in 52–77% yields (Scheme 1). Tandem reduction–olefination of phosphonoacetates **6a–f** with $NaBH_4$ (1 mol equiv) in EtOH was then examined, as shown in Scheme 1 and Table 1. In the case of phosphonoacetate **6a**, $NaBH_4$ (1 mol equiv) was added to the solution of **6a** in EtOH at −78 °C, and the mixture was then stirred for 2 h, after which the temperature was allowed to rise to room temperature. After 1 h of stirring at room temperature, (*Z*)-α-fluoro-α,β-unsaturated ester (*Z*)-**7a** was obtained in 83% yield as the sole stereoisomer (Table 1, entry 1). Excellent *Z*-selectivity was also achieved in all the other tandem reduction–olefination reactions with phosphonoacetates **6b–f** (Table 1, entries 2–6). The disappearance of the starting phosphonoacetates **6a–f** was conveniently monitored by thin-layer chromatographic (TLC) analysis, and after that the reaction temperature was raised to complete the olefination of the resulting pro-(*Z*)-oxyanion intermediate (Fig. 2). The reduction of phosphonoacetates **6c**,**d** with bulky acyl groups was slower than that of phosphonoacetates **6a**,**b**,**e**,**f**, and the tandem reduction–olefination of phosphonoacetate **6d** was achieved at −78 °C for 18 h without an increase in temperature (Table 1, entries 3 and 4). High volatility of (*Z*)-α-fluoro-α,β-unsaturated ester (*Z*)-**7d** caused an inaccurate yield (Table 1, entry 4). Moderate yields of (*Z*)-α-fluoro-α,β-unsaturated esters (*Z*)-**7e**,**f** were probably attributable to the high lability of the starting phosphonoacetates **6e**,**f** (Table 1, entries 5 and 6).

Table 1. Tandem reduction–olefination of **6a–f** with $NaBH_4$[a]

Entry	Phosphonoacetate	Temperature/time	Yield (%)[b]	*E*:*Z*[c]
1	**6a**	−78 °C/2 h to rt/1 h	83 (**7a**)	0:100 (**7a**)
2	**6b**	−78 °C/2 h to rt/1 h	76 (**7b**)	<1:>99 (**7b**)
3	**6c**	−78 °C/18 h to rt/1 h	84 (**7c**)	9:91 (**7c**)
4	**6d**	−78 °C/18 h	58 (**7d**)[d]	4:96 (**7d**)
5	**6e**[e]	−78 °C/2 h to rt/1 h	59 (**7e**)	0:100 (**7e**)
6	**6f**[e]	−78 °C/1 h to rt/1 h	63 (**7f**)	<1:>99 (**7f**)

[a] EtOH, **6**/$NaBH_4$ (1:1 molar ratio).
[b] Isolated yields.
[c] Determined by ^{1}H NMR (300 or 400 MHz, $CDCl_3$) analysis.
[d] High volatility.
[e] Labile compounds.

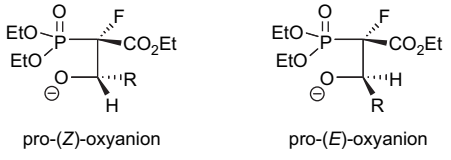


Figure 2. Pro-(*Z*)- and pro-(*E*)-oxyanion intermediate in tandem reduction–olefination of **6a–f**.

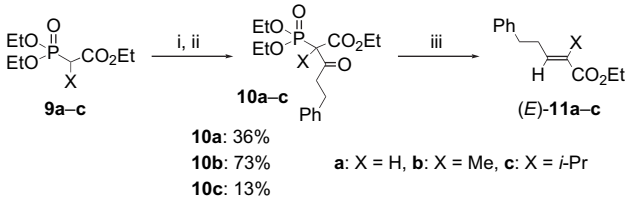
On the other hand, ordinary *E*-selective HWE reactions of phosphonoacetate **3** with aldehydes **8a–f** were performed under *n*-BuLi conditions at room temperature. As anticipated, (*E*)-α-fluoro-α,β-unsaturated esters (*E*)-**7a–f** were obtained as major products in each corresponding reaction (Scheme 1, Table 2). That is to say, a complementarity of stereoselectivity was found between the HWE reaction of phosphonoacetate **3** with aldehydes **8a–f** and the tandem reduction–olefination of phosphonoacetate **6a–f**. The geometry and the diastereomeric ratios of olefins **7a–f** were confirmed on the basis of the coupling constants between fluorine and the adjacent olefinic proton ($^3J_{H,F}$), and the integration of appropriate proton absorptions was obtained by ^{1}H NMR (300 or 400 MHz) analysis, respectively.

Table 2. HWE reactions of 2-fluoro-2-phosphonoacetate **3** with aldehydes **8a–f**[a]

Entry	Aldehyde	Yield (%)[b]	*E*:*Z*[c]
1	**8a**	78 (**7a**)	88:12 (**7a**)
2	**8b**	77 (**7b**)	92:8 (**7b**)[e]
3	**8c**	81 (**7c**)	91:9 (**7c**)
4	**8d**	37 (**7d**)[d]	97:3 (**7d**)[e]
5	**8e**	84 (**7e**)	93:7 (**7e**)
6	**8f**	93 (**7f**)	89:11 (**7f**)

[a] THF, rt, 20 h, **3**/*n*-BuLi/**8** (1.2:1.2:1 molar ratio).
[b] Isolated yields.
[c] Determined by ^{1}H NMR (300 or 400 MHz, $CDCl_3$) analysis.
[d] High volatility.
[e] Determined by ^{1}H NMR (400 MHz, C_6D_6) analysis.

We also subjected a series of phosphonoacetates **9a–c** to the tandem reduction–olefination. Phosphonoacetates **10a–c** were prepared by the treatment of phosphonoacetates **9a–c** with *n*-BuLi (1.05 mol equiv) in THF at 0 °C, followed by acylation of the resulting lithium enolate with 3-phenylpropionyl chloride (**5b**) (1.05 mol equiv) (Scheme 2). Under



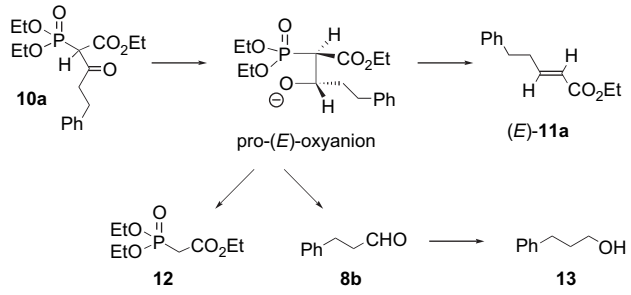
Scheme 2. Reagents and conditions: (i) *n*-BuLi, THF, 0 °C, 1 h; (ii) $PhCH_2CH_2COCl$ (**5b**), THF, 0 °C, **a**: 30 min, **b**: 3 h, **c**: 20 h; (iii) $NaBH_4$, EtOH, −78 °C to rt (Table 3).

Table 3. Tandem reduction–olefination of **10a–c** with $NaBH_4$[a]

Entry	Phosphonoacetate	Temperature/time	Yield (%)[b]	*E*:*Z*[c]
1	**10a**	−78 °C/2 h to rt/1 h	48 (**11a**)[d]	100:0 (**11a**)
2	**10b**	−78 °C/20 h to rt/1 h	49 (**11b**)	93:7 (**11b**)
3	**10c**	−78 °C/6 h	—[e]	—
4	**10c**	0 °C/20 h	9 (**11c**)	56:44 (**11c**)

[a] EtOH, **10**/$NaBH_4$ (1:1 molar ratio).
[b] Isolated yields.
[c] Determined by ^1H NMR (400 MHz, $CDCl_3$) analysis.
[d] 3-Phenyl-1-propanol (19%) was obtained.
[e] No reaction.

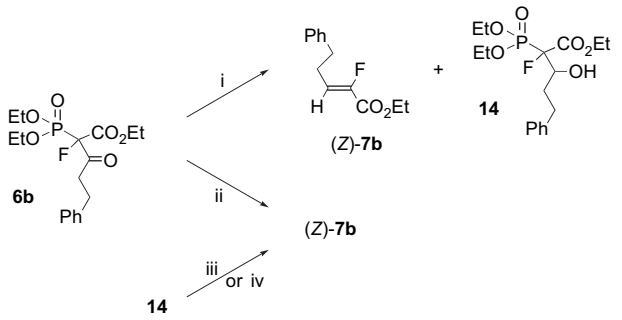
the same reaction conditions of the tandem reduction–olefination described above, phosphonoacetates **10a**,**b** provided α,β-unsaturated esters **11a**,**b** in *E*:*Z* ratios of 100:0 and 93:7, respectively (Table 3, entries 1 and 2). According to Cahn–Ingold–Prelog (CIP) priority, each major stereoisomer of α,β-unsaturated esters **11a**,**b** was assigned as the *E*-configuration, while (*E*)-**11a**,**b** and (*Z*)-**7a–f** refer to the same geometry. Thus, the olefinic proton and the ester moiety of (*E*)-**11a**,**b** and (*Z*)-**7a–f** are on the same side of the double bond. However, the reaction of phosphonoacetate **10c** with a bulky isopropyl group instead of the H, F, or Me group appeared to suffer, as indicated by the low stereoselectivity and the low yield (Table 3, entries 3 and 4). The geometry of olefin **11a** was confirmed on the basis of the coupling constants ($^3J_{H,H}$=15.6 Hz) of ^1H NMR (400 MHz) analysis between both olefinic protons. The geometry of olefins **11b**,**c** was determined on the basis of the chemical shift of the olefinic proton by application of Tobey–Pascual substituent shielding constants.[50–52] The diastereomeric ratios of olefins **11a–c** were also confirmed on the basis of the integration of appropriate proton absorptions by ^1H NMR (400 MHz) analysis. It is worth noting that the tandem reaction of **10a** with $NaBH_4$ afforded 3-phenyl-1-propanol (**13**) in 19% yield as a by-product together with 48% of (*E*)-α,β-unsaturated ester (*E*)-**11a** (Table 3, entry 1). That is to say, reduction of phosphonoacetate **10a** furnished the pro-(*E*)-oxyanion intermediate, from which a retro-aldol type reaction would take place under the basic conditions to give the 3-phenylpropionaldehyde (**8b**). The aldehyde **8b** would be reduced by $NaBH_4$ to 3-phenyl-1-propanol (**13**), immediately (Scheme 3).



Scheme 3. Tandem reduction–olefination of **10a** and by-product **13**.

2.2. Mechanistic consideration of tandem reduction–olefination

As stated above, we performed the reduction step in the tandem reduction–olefination of phosphonoacetates **6a–f** at −78 °C to better differentiate a transition state for the diastereoselective reduction with $NaBH_4$. In fact, Burton and Thenappan reported in 1991 that the use of $NaBH_4$ as a reducing agent of **6e** at room temperature led to a mixture of two geometrical isomers (*E*:*Z*=52:48).[53] In our experiment, an apparent decrease in *Z*-selectivity (*E*:*Z*=16:84, 63% yield) was also found in the tandem reduction–olefination of **6b** at room temperature (Scheme 4).



Scheme 4. Reagents and conditions: (i) $NaBH_4$, EtOH, −78 °C, 18 h; (ii) $NaBH_4$, EtOH, rt, 2 h; (iii) $NaBH_4$, EtOH, rt, 1 h; (iv) *n*-BuLi, THF, rt, 1 h.

Next, we tried to isolate the oxyanion intermediate of the tandem reduction–olefination reaction of **6a–f**. In the case of **6b**, the tandem reduction–olefination at −78 °C gave a fortuitous mixture of (*Z*)-**7b** and alcohol **14**. Chromatographic separation and isolation of the products afforded (*Z*)-**7b** (44%, *E*:*Z*=<1:>99) and alcohol **14** (46%), as shown in Scheme 4. ^{13}C NMR analysis (75 MHz) of alcohol **14** strongly suggested that the alcohol was obtained in a diastereomerically pure form. In addition, treatment of alcohol **14** with $NaBH_4$ (1 mol equiv) in EtOH at room temperature resulted in the formation of (*Z*)-**7b** with an *E*:*Z* ratio of <1:>99 in 80% yield. On the other hand, the addition of *n*-BuLi (1 mol equiv) to a solution of alcohol **14** in THF at room temperature gave (*Z*)-**7b** in 80% yield with a slightly lower stereoselectivity (*E*:*Z*=8:92). It can therefore be presumed that a retro-aldol type reaction is involved here that is similar to the reaction of **10a**. Unfortunately, 3-phenyl-1-propanol (**13**) was not obtained as a by-product in the reaction with $NaBH_4$. A decrease in the stereoselectivity of the olefination of alcohol **14** under *n*-BuLi conditions compared with that under $NaBH_4$ conditions may be ascribed to the ordinary *E*-selective HWE reaction of a small amount of aldehyde **8b** with phosphonoacetate **3** formed by a retro-aldol type reaction of pro-(*Z*)-oxyanion intermediate.

On the basis of the experimental results described above, excellent *Z*-selectivity of this tandem reduction–olefination of **6a–f** to α-fluoro-α,β-unsaturated esters **7a–f** should be the result of highly diastereoselective reduction. When a possible Felkin–Anh type transition state is envisioned,[54–60] the attack of hydride preferentially involves the conformation **A** of phosphonoacetates **6a–f**, not **B**, to minimize steric interactions, as indicated in the Newman projections (Fig. 3). This Felkin–Anh model considers that the transition state mostly resembles the ketones and hydrides.[61] The tandem reduction–olefination of **10a**,**b** to α,β-unsaturated esters **11a**,**b** is also stereoselective, and the stereoselective outcome may be understood in terms of the similar Felkin–Anh type conformation of **10a**,**b** (conformation **C**), as shown in Figure 3. In the case of phosphonoacetate **10c** (X=*i*-Pr),

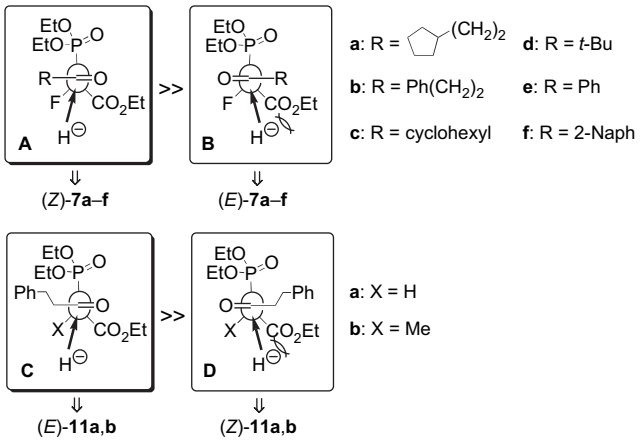


Figure 3. Plausible conformations of **6a**–**f** and **10a**,**b** for diastereoselective reduction with $NaBH_4$.

the reduction is slightly stereoselective because the two possible conformations **C** and **D** are equally important.

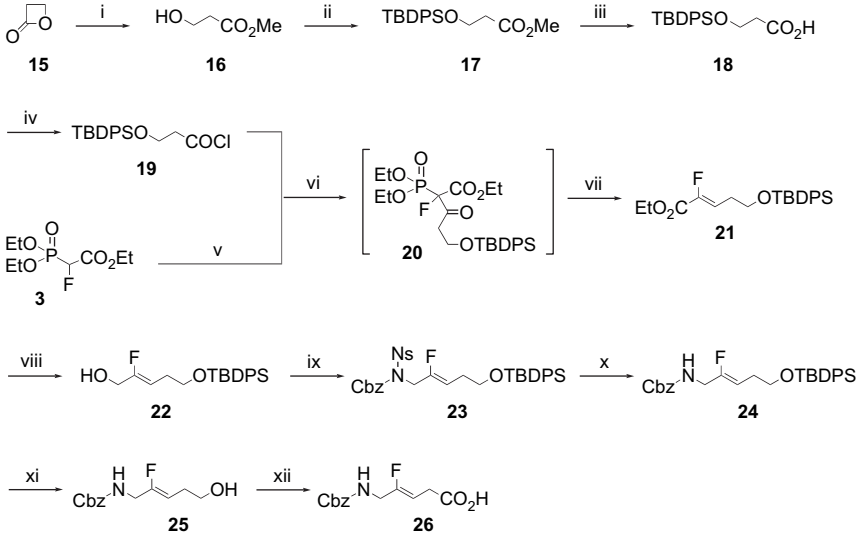
2.3. Synthesis of Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly as a dipeptide isostere

The chemistry described above was extended to the preparation of dipeptide isosteres. A possible strategy for the synthesis of Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly (**26**) as a dipeptide isostere via *Z*-selective tandem reduction–olefination of triethyl 2-acyl-2-fluoro-2-phosphonoacetate **20** with $NaBH_4$ is shown in Scheme 5. Our synthesis began with a ring opening reaction of the commercially available β-propiolactone (**15**), followed by protection of the resultant alcohol **16** with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of imidazole according to the procedure of Ley and co-workers (96% yield).[62] Alkaline hydrolysis of the methyl ester **17** with aqueous EtOH solution of NaOH furnished carboxylic acid **18** (99% yield). Upon treatment with oxalyl chloride in CH_2Cl_2, carboxylic acid **18** provided the desired acyl chloride **19** in a quantitative yield. Acylation of phosphonoacetate **3** then afforded triethyl 2-acyl-2-fluoro-2-phosphonoacetate **20** via treatment with acyl chloride **19** under *n*-BuLi conditions at −78 °C in THF. As expected, phosphonoacetate **20** was easily converted to (*Z*)-α-fluoro-α,β-unsaturated ester **21** by the tandem reduction–olefination with $NaBH_4$ in EtOH with excellent stereoselectivity (*E*:*Z*=0:100) at −78 °C in 63% yield (two steps).

Reduction of the (*Z*)-α-fluoro-α,β-unsaturated ester **21** gave the corresponding primary alcohol **22** in 93% yield. The hydroxyl group of **22** was successively transformed to the protected amino group of **23** under Mitsunobu reaction conditions.[63–65] In this reaction, PPh_3, *N*-carbobenzoxy-2-nitrobenzenesulfonamide (*N*-Cbz-NsNH), and alcohol **22** were dissolved in CH_2Cl_2 and diethyl azodicarboxylate (DEAD) in toluene was slowly added to the solution. However, when DEAD was first reacted with the phosphine, a poor result was obtained. Next, Cbz-protected **24** was obtained in 95% yield (two steps) by chemoselective deprotection of the 2-nitrobenzenesulfonyl (Ns) group of **23** with 4-*tert*-butylthiophenol in the presence of K_2CO_3 in DMF. Deprotection of the TBDPS group of **24** with tetra-*n*-butylammonium fluoride (TBAF) in THF cleanly produced the primary alcohol **25** in 92% yield. Finally, oxidation of alcohol **25** with an excess amount of Jones reagent in acetone delivered Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly (**26**) as a dipeptide isostere in 80% yield.

3. Conclusion

We described here the tandem reduction–olefination of 2-acyl-2-fluoro-2-phosphonoacetates **6a**–**f**, as a novel one-pot reaction, for the preparation of α-fluoro-α,β-unsaturated esters **7a**–**f** with excellent *Z*-selectivity. Furthermore, a concise synthesis of Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly (**26**) as a dipeptide isostere was achieved by virtue of an application of this reaction.



Scheme 5. Reagents and conditions: (i) NaOMe, MeOH, 50 °C, 4 h; (ii) TBDPSCl, imidazole, CH_2Cl_2, rt, 14 h; (iii) 1 N NaOH, EtOH, rt, 6 h; (iv) $(COCl)_2$, CH_2Cl_2, rt, 15 h; (v) *n*-BuLi, THF, −78 °C, 1 h; (vi) **19**, THF, −78 °C, 1 h; (vii) $NaBH_4$, EtOH, −78 °C, 2 h to rt, 1 h; (viii) $LiAlH_4$, THF, 0 °C, 30 min; (ix) PPh_3, *N*-Cbz-NsNH, DEAD, CH_2Cl_2, rt, 1 h; (x) 4-*tert*-BuC_6H_4SH, K_2CO_3, DMF, rt, 15 min; (xi) TBAF, THF, rt, 45 min; (xii) Jones reagent, acetone, rt, 30 min.

4. Experimental

4.1. General

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-420 IR Fourier transform spectrometer. ^{1}H NMR (400 or 300 MHz) and ^{13}C NMR (100 or 75 MHz) spectra were recorded on JEOL JNM-AL400 and JEOL JNM-AL300 spectrometers, respectively. Chemical shifts are given in δ values (parts per million) using tetramethylsilane (TMS) as an internal standard. Electron impact mass spectra (EIMS) were recorded on a JEOL JMS SX-102A spectrometer. Electron spray ionization mass spectra (ESIMS) were recorded on a Waters LCT Premier spectrometer. Elemental combustion analyses were performed using a Yanagimoto CHN CORDER MT-5. All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F_{254}). Preparative TLC (PTLC) was performed on 0.5-mm silica gel plates (Merck 5744; 60 F_{254}). Column chromatography was carried out on silica gel [Kanto Chemical 60N (spherical, neutral); 63–210 μm]. Anhydrous THF, CH_2Cl_2, MeOH, and DMF were used as purchased from Kanto Chemical. Anhydrous EtOH was commercially obtained from Wako Pure Chemical Industry. All aldehydes and acyl chlorides were distilled prior to use. All other reagents were used as purchased.

4.2. Acylation of triethyl 2-fluoro-2-phosphonoacetate (3) with 3-phenylpropionyl chloride (5b)

A 1.6 mol/l solution of *n*-BuLi (4.9 ml, 13.0 mmol) in *n*-hexane was added to a stirred solution of phosphonoacetate **3** (1.5 ml, 12.4 mmol) in anhydrous THF (20 ml) at 0 °C under argon. The mixture was stirred at 0 °C for 1 h, and then 3-phenylpropionyl chloride (**5b**) (1.16 ml, 13.0 mmol) was slowly added to the solution. After being stirred at 0 °C for 1 h, the reaction mixture was treated with 5% HCl (10 ml) and then extracted with AcOEt (50 ml×3). The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by silica gel column chromatography [*n*-hexane–AcOEt (1:1)] to afford **6b** (1.68 g, 60%) as a colorless oil.

4.2.1. Triethyl 5-cyclopentyl-2-fluoro-3-oxo-2-phosphonopentanoate (6a). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02–1.15 (2H, m), 1.31–1.41 (9H, m), 1.45–1.82 (9H, m), 2.77 (2H, dt, J=3.2, 7.3 Hz), 4.23–4.40 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (s), 16.3 (d, $^3J_{C,P}$=6.2 Hz), 16.4 (d, $^3J_{C,P}$=6.2 Hz), 25.1 (s), 28.9 (d, ^3J=2.5 Hz), 32.5 (s), 37.9 (s), 39.4 (s), 63.4 (s), 65.2 (d, $^2J_{C,P}$=6.9 Hz), 65.3 (d, $^2J_{C,P}$=6.9 Hz), 98.5 (dd, $^1J_{C,F}$=208.6 Hz, $^1J_{C,P}$=155.7 Hz), 162.2 (d, $^2J_{C,F}$=23.7 Hz), 199.0 (d, $^2J_{C,F}$=23.0 Hz); IR (neat) 1758, 1733, 1270, 1022 cm^{-1}; EIMS calcd for $C_{16}H_{28}FO_6P$ MW 366.1608, found *m/z* 366.1606 (M^+).

4.2.2. Triethyl 2-fluoro-3-oxo-5-phenyl-2-phosphonopentanoate (6b). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.40 (9H, m), 2.90–2.97 (2H, m), 3.07–3.14 (2H, m), 4.18–4.35 (6H, m), 7.15–7.33 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (s), 16.3 (d, $^3J_{C,P}$=6.2 Hz), 28.8 (d, ^3J=2.5 Hz), 40.2 (s), 63.3 (s), 65.2 (d, $^2J_{C,P}$=6.9 Hz), 65.3 (d, $^2J_{C,P}$=6.9 Hz), 98.5 (dd, $^1J_{C,F}$=208.6 Hz, $^1J_{C,P}$=154.4 Hz), 126.3 (s), 128.4 (s), 128.5 (s), 140.2 (s), 162.0 (d, $^2J_{C,F}$=22.4 Hz), 197.8 (d, $^2J_{C,F}$=23.0 Hz); IR (neat) 1757, 1732, 1265, 1018 cm^{-1}; EIMS calcd for $C_{17}H_{24}FO_6P$ MW 374.1295, found *m/z* 374.1295 (M^+). Anal. Calcd for $C_{17}H_{24}FO_6P$: C, 54.54; H, 6.46. Found: C, 54.57; H, 6.46%.

4.2.3. Triethyl 3-cyclohexyl-2-fluoro-3-oxo-2-phosphonopropanoate (6c). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13–1.49 (14H, m), 1.63–1.96 (5H, m), 2.98–3.10 (1H, m), 4.25–4.40 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (s), 16.4 (d, $^3J_{C,P}$=6.2 Hz), 25.3 (s), 25.6 (s), 25.7 (s), 28.1 (s), 28.6 (d, ^4J=1.2 Hz), 46.4 (s), 63.3 (s), 65.1 (d, $^2J_{C,P}$=6.9 Hz), 65.2 (d, $^2J_{C,P}$=6.9 Hz), 98.5 (dd, $^1J_{C,F}$=209.3 Hz, $^1J_{C,P}$=156.3 Hz), 162.3 (d, $^2J_{C,F}$=22.4 Hz), 201.8 (d, $^2J_{C,F}$=22.4 Hz); IR (neat) 1756, 1726, 1271, 1097, 1022 cm^{-1}; EIMS calcd for $C_{15}H_{26}FO_6P$ MW 352.1451, found *m/z* 352.1473 (M^+). Anal. Calcd for $C_{15}H_{26}FO_6P$: C, 51.13; H, 7.44. Found: C, 50.97; H, 7.30%.

4.2.4. Triethyl 2-fluoro-4,4-dimethyl-3-oxo-2-phosphonopentanoate (6d). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (9H, d, J=1.7 Hz), 1.25–1.45 (9H, m), 4.25–4.45 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (s), 16.4 (d, $^3J_{C,P}$=6.2 Hz), 25.8 (d, $^4J_{C,F}$=5.0 Hz), 45.8 (dd, ^3J=2.5, 3.7 Hz), 63.3 (s), 65.0 (d, $^2J_{C,P}$=6.9 Hz), 65.1 (d, $^2J_{C,P}$=6.9 Hz), 99.9 (dd, $^1J_{C,F}$=214.2 Hz, $^1J_{C,P}$=158.8 Hz), 162.5 (d, $^2J_{C,F}$=22.4 Hz), 203.6 (d, $^2J_{C,F}$=21.8 Hz); IR (neat) 1752, 1716, 1268, 1245, 1022 cm^{-1}; EIMS calcd for $C_{13}H_{24}FO_6P$ MW 326.1295, found *m/z* 326.1308 (M^+). Anal. Calcd for $C_{13}H_{24}FO_6P$: C, 47.85; H, 7.41. Found: C, 47.41; H, 7.18%.

4.2.5. Triethyl 2-fluoro-3-oxo-2-phosphono-3-phenylpropanoate (6e). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, J=7.1 Hz), 1.32–1.41 (6H, m), 4.22–4.46 (6H, m), 7.42–7.55 (2H, m), 7.57–7.65 (1H, m), 7.95–8.03 (1H, m), 8.07–8.14 (1H, m); ESIMS calcd for $C_{15}H_{21}FO_6P$ MW 347.1060, found *m/z* 347.1031 (M^++H).

4.2.6. Triethyl 2-fluoro-3-(2-naphthyl)-3-oxo-2-phosphonopropanoate (6f). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, J=7.1 Hz), 1.32–1.43 (6H, m), 4.14–4.51 (6H, m), 7.53–7.67 (2H, m), 7.83–7.93 (2H, m), 7.94–8.03 (2H, m), 8.60 (1H, s); ESIMS calcd for $C_{19}H_{23}FO_6P$ MW 397.1216, found *m/z* 397.1190 (M^++H).

4.2.7. Triethyl 3-oxo-5-phenyl-2-phosphonopentanoate (10a). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.39 (9H, m, keto- and enol-tautomer), 2.86–3.36 (4H, m, keto- and enol-tautomer), 3.86–4.33 (6H, m, keto- and enol-tautomer), 3.86–4.33 (1H, m, keto-tautomer), 7.14–7.33 (5H, m, keto- and enol-tautomer), 13.70 (1H, s, enol-tautomer); IR (neat) 1738, 1703, 1580, 1433, 1236, 1077, 1025, 976 cm^{-1}; EIMS calcd for $C_{17}H_{25}O_6P$ MW 356.1389, found *m/z* 356.1403 (M^+).

4.2.8. Triethyl 2-methyl-3-oxo-5-phenyl-2-phosphonopentanoate (10b). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.36 (9H, m), 1.63 (3H, d, $^3J_{H,P}$=15.6 Hz), 2.89–3.17 (4H, m), 4.08–4.28 (6H, m), 7.15–7.34 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (s), 16.3 (d, $^3J_{C,P}$=6.2 Hz), 16.4 (d, $^3J_{C,P}$=6.2 Hz), 17.1 (d, $^2J_{C,P}$=5.6 Hz),

30.0 (s), 42.0 (s), 62.2 (s), 63.4 (d, $^1J_{C,P}$=133.3 Hz), 63.3 (d, $^2J_{C,P}$=6.9 Hz), 63.5 (d, $^2J_{C,P}$=6.9 Hz), 126.1 (s), 128.4 (s), 128.5 (s), 140.9 (s), 168.5 (d, $^2J_{C,P}$=3.7 Hz), 200.8 (d, $^2J_{C,P}$=1.9 Hz); IR (neat) 1732, 1716, 1455, 1257, 1106, 1048, 1021, 970 cm^{-1}; EIMS calcd for $C_{18}H_{27}O_6P$ MW 370.1545, found *m/z* 370.1546 (M^+).

4.2.9. Triethyl 2-isopropyl-3-oxo-5-phenyl-2-phosphonopentanoate (10c). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, d, *J*=6.8 Hz), 1.19 (3H, d, *J*=6.8 Hz), 1.25–1.38 (9H, m), 2.61–2.77 (1H, m), 2.86–3.05 (4H, m), 4.05–4.31 (4H, m), 4.25 (2H, q, *J*=7.1 Hz), 7.10–7.34 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (s), 16.3 (d, $^3J_{C,P}$=2.5 Hz), 16.4 (d, $^3J_{C,P}$=1.9 Hz), 19.0 (d, $^3J_{C,P}$=7.5 Hz), 19.1 (d, $^3J_{C,P}$=5.0 Hz), 30.2 (s), 32.7 (d, $^2J_{C,P}$=3.1 Hz), 63.0 (d, $^2J_{C,P}$=6.9 Hz), 63.3 (d, $^2J_{C,P}$=7.5 Hz), 72.1 (d, $^1J_{C,P}$=129.5 Hz), 126.1 (s), 128.42 (s), 128.45 (s), 167.8 (d, $^2J_{C,P}$=3.7 Hz), 201.4 (d, $^2J_{C,P}$=1.9 Hz); IR (neat) 1716, 1255, 1226, 1047, 967 cm^{-1}; EIMS calcd for $C_{20}H_{31}O_6P$ MW 398.1858, found *m/z* 398.1877 (M^+).

4.3. Tandem reduction–olefination of triethyl 5-cyclopentyl-2-fluoro-3-oxo-2-phosphonopentanoate (6a)

To a solution of phosphonoacetate **6a** (100 mg, 0.273 mmol) in EtOH (7 ml) was added a solution of $NaBH_4$ (10.3 mg, 0.273 mmol) in EtOH (3 ml) at −78 °C under argon. After stirring at −78 °C for 2 h, the reaction mixture was allowed to warm to room temperature and then was stirred for 1 h. The mixture was treated with aqueous solution saturated with NH_4Cl (5 ml) and then extracted with AcOEt (20 ml×3). The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue (*E*:*Z*=0:100) was purified by silica gel column chromatography [*n*-hexane–AcOEt (19:1)] to afford (*Z*)-**7a** (48 mg, 83%) as a colorless oil.

4.3.1. Ethyl (*Z*)-5-cyclopentyl-2-fluoro-2-pentenoate [(*Z*)-7a]. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00–1.20 (2H, m), 1.33 (3H, t, *J*=7.1 Hz), 1.39–1.68 (6H, m), 1.70–1.87 (3H, m), 2.52 (2H, q, *J*=7.6 Hz), 4.28 (2H, q, *J*=7.1 Hz), 6.13 (1H, dt, $^3J_{H,F}$=33.5 Hz, $^3J_{H,H}$=8.1 Hz); IR (neat) 1735, 1679, 1455, 1371, 1311, 1083 cm^{-1}; EIMS calcd for $C_{12}H_{19}FO_2$ MW 214.1369, found *m/z* 214.1348 (M^+). Anal. Calcd for $C_{12}H_{19}FO_2$: C, 67.26; H, 8.94. Found: C, 66.89; H, 8.82%.

4.3.2. Ethyl (*Z*)-2-fluoro-5-phenyl-2-pentenoate [(*Z*)-7b].[66,67,71] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, t, *J*=7.1 Hz), 2.51–2.61 (2H, m), 2.76 (2H, t, *J*=7.3 Hz), 4.27 (2H, q, *J*=7.1 Hz), 6.14 (1H, dt, $^3J_{H,F}$=33.2 Hz, $^3J_{H,H}$=7.6 Hz), 7.10–7.34 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 26.0 (d, $^3J_{C,F}$=2.5 Hz), 34.45 (d, $^4J_{C,F}$=1.9 Hz), 61.5, 119.5 (d, $^2J_{C,F}$=11.2 Hz), 126.29, 128.20, 128.31, 128.53, 140.59, 148.21 (d, $^1J_{C,F}$=256.6 Hz), 160.8 (d, $^2J_{C,F}$=35.5 Hz); IR (neat) 1733, 1679, 1455, 1371, 1313, 1105 cm^{-1}; EIMS calcd for $C_{13}H_{15}FO_2$ MW 222.1056, found *m/z* 222.1051 (M^+). Anal. Calcd for $C_{13}H_{15}FO_2$: C, 70.25; H, 6.80. Found: C, 69.79; H, 6.74%.

4.3.3. Ethyl (*Z*)-3-cyclohexyl-2-fluoro-2-propenoate [(*Z*)-7c].[68] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09–1.42 (9H, m), 1.60–1.82 (5H, m), 2.49–2.64 (1H, m), 4.27 (1H, q, *J*=7.2 Hz), 5.98 (1H, dd, $^3J_{H,F}$=33.9 Hz, $^3J_{H,H}$=9.7 Hz); IR (neat) 2929, 2854, 1736, 1673, 1304, 1087 cm^{-1}; EIMS calcd for $C_{11}H_{17}FO_2$ MW 200.1213, found *m/z* 200.1218 (M^+).

4.3.4. Ethyl (*Z*)-2-fluoro-4,4-dimethyl-2-pentenoate [(*Z*)-7d].[69,70] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (9H, d, *J*=0.7 Hz), 1.33 (3H, t, *J*=7.2 Hz), 4.26 (2H, q, *J*=7.2 Hz), 6.06 (1H, d, $^3J_{H,F}$=38.7 Hz); IR (neat) 1735, 1671, 1282, 1205, 1095 cm^{-1}; EIMS calcd for $C_9H_{15}FO_2$ MW 174.1056, found *m/z* 174.1060 (M^+).

4.3.5. Ethyl (*Z*)-2-fluoro-3-phenyl-2-propenoate [(*Z*)-7e].[67,68] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, t, *J*=7.1 Hz), 4.36 (2H, q, *J*=7.1 Hz), 6.92 (1H, d, $^3J_{H,F}$=35.2 Hz), 7.33–7.44 (3H, m), 7.61–7.68 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 61.9, 117.5 (d, $^2J_{C,F}$=4.4 Hz), 128.8, 129.7, 130.3 (d, $^4J_{C,F}$=8.1 Hz), 131.2 (d, $^3J_{C,F}$=4.4 Hz), 148.6 (d, $^1J_{C,F}$=267.2 Hz), 161.4 (d, $^2J_{C,F}$=34.3 Hz); IR (neat) 3060, 2983, 2939, 1730, 1660, 1496, 1450, 1371, 1282, 1201, 1101 cm^{-1}; ESIMS calcd for $C_{11}H_{11}NaFO_2$ MW 217.0641, found *m/z* 217.0626 (M^++Na).

4.3.6. Ethyl (*Z*)-2-fluoro-3-(2-naphthyl)-2-propenoate [(*Z*)-7f]. Colorless solid ($CHCl_3$–*n*-hexane), mp 60–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 1.41 (3H, t, *J*=7.1 Hz), 4.38 (2H, q, *J*=7.1 Hz), 7.09 (1H, d, $^3J_{H,F}$=35.2 Hz), 7.45–7.57 (2H, m), 7.75–7.91 (4H, m), 8.10 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 61.9, 117.7 (d, $^2J_{C,F}$=5.0 Hz), 126.6, 126.8 (d, $^4J_{C,F}$=8.1 Hz), 127.3, 127.7, 128.5, 128.6, 128.68, 128.74, 130.8 (d, $^4J_{C,F}$=8.1 Hz), 133.4 (d, $^3J_{C,F}$=33.0 Hz), 147.2 (d, $^1J_{C,F}$=267.8 Hz), 161.5 (d, $^2J_{C,F}$=34.2 Hz); IR (KBr) 3421, 3371, 3062, 2985, 1726, 1655, 1373, 1254, 1099, 1022 cm^{-1}; ESIMS calcd for $C_{15}H_{14}FO_2$ MW 245.0978, found *m/z* 245.0983 (M^++H). Anal. Calcd for $C_{15}H_{13}FO_2$: C, 73.76; H, 5.36. Found: C, 73.43; H, 5.55%.

4.3.7. Ethyl (*E*)-5-phenyl-2-pentenoate [(*E*)-11a].[72] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, t, *J*=7.1 Hz), 2.45–2.61 (2H, m), 2.71–2.86 (2H, m), 4.18 (2H, q, *J*=7.1 Hz), 5.85 (1H, d, *J*=15.6 Hz), 7.00 (1H, dt, *J*=6.6, 15.6 Hz), 7.14–7.40 (5H, m); IR (neat) 1719, 1653, 1267, 1197, 1039 cm^{-1}; EIMS calcd for $C_{13}H_{16}O_2$ MW 204.1150, found *m/z* 204.1121 (M^+). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.19; H, 7.92%.

4.3.8. Ethyl (*E*)-2-methyl-5-phenyl-2-pentenoate [(*E*)-11b].[73] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, t, *J*=7.1 Hz), 1.78 (3H, s), 2.41–2.56 (2H, m), 2.69–2.82 (2H, m), 4.19 (2H, q, *J*=7.1 Hz), 6.81 (1H, dt, *J*=1.2, 7.3 Hz), 7.15–7.33 (5H, m); IR (neat) 1709, 1649, 1266, 1116, 1080 cm^{-1}; EIMS calcd for $C_{14}H_{18}O_2$ MW 218.1307, found *m/z* 218.1281 (M^+). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.75; H, 8.33%.

4.3.9. Ethyl (*Z*)-2-methyl-5-phenyl-2-pentenoate [(*Z*)-11b].[74] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, t, *J*=7.1 Hz), 1.89 (3H, d, *J*=1.2 Hz), 2.68–2.83 (4H, m), 4.19 (2H, q, *J*=7.1 Hz), 5.96 (1H, dt, *J*=1.2, 7.1 Hz), 7.15–7.33 (5H, m); IR (neat) 1702, 1652, 1125, 1028 cm^{-1}; EIMS calcd for $C_{14}H_{18}O_2$ MW 218.1307, found *m/z* 218.1304 (M^+). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.63; H, 8.36%.

4.3.10. Mixture of ethyl (*E*)-2-isopropyl-5-phenyl-2-pentanoate [(*E*)-11c] and ethyl (*Z*)-2-isopropyl-5-phenyl-2-pentanoate [(*Z*)-11c].[75] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (6H, d, J=6.8 Hz, *E*-isomer), 1.11 (6H, d, J=6.8 Hz, *Z*-isomer), 1.30 (3H, t, J=7.1 Hz, *E*- and *Z*-isomer), 2.45–2.91 (5H, m, *E*- and *Z*-isomer), 4.11–4.27 (2H, m, *E*- and *Z*-isomer), 5.73 (1H, t, J=7.3 Hz, *Z*-isomer), 6.61 (1H, t, J=7.1 Hz, *E*-isomer), 7.11–7.36 (5H, m, *E*- and *Z*-isomer); EIMS calcd for $C_{16}H_{22}O_2$ MW 246.1620, found *m/z* 246.1598 (M^+). Anal. Calcd for $C_{14}H_{18}O_2$: C, 78.01; H, 9.00. Found: C, 77.66; H, 9.01%.

4.3.11. Ethyl 2-diethylphosphono-2-fluoro-3-hydroxy-5-phenylpentanoate (14). Colorless prism (Et_2O–*n*-hexane), mp 66.5–67.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, t, J=7.0 Hz), 1.32 (3H, t, J=7.0 Hz), 1.34 (3H, t, J=7.0 Hz), 1.54–1.71 (1H, m), 1.93–2.11 (1H, m), 2.60–2.79 (1H, m), 2.85–3.03 (1H, m), 3.40 (1H, br s), 4.09–4.42 (7H, m) 7.10–7.34 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (s), 16.25 (d, $^3J_{C,P}$=5.3 Hz), 16.28 (d, $^3J_{C,P}$=5.3 Hz), 31.6 (d, $^4J_{C,F}$=1.3 Hz), 32.2 (dd, $^3J_{C,F}$=4.7 Hz, $^3J_{C,P}$=8.4 Hz), 62.4 (s), 64.2 (d, $^2J_{C,P}$=6.9 Hz), 64.6 (dd, $^4J_{C,F}$=1.3 Hz, $^2J_{C,P}$=6.9 Hz), 71.8 (d, $^2J_{C,F}$=19.9 Hz), 98.0 (dd, $^1J_{C,F}$=204.9 Hz, $^1J_{C,P}$=160.7 Hz), 125.9 (s), 128.3 (s), 128.4 (s), 141.2 (s), 165.8 (dd, $^2J_{C,F}$=22.7 Hz, $^2J_{C,P}$=2.2 Hz); IR (KBr) 3314, 1756, 1601, 1444, 1396, 1255 cm^{-1}; EIMS calcd for $C_{17}H_{26}O_6FP$ MW 379.1451, found *m/z* 376.1439 (M^+). Anal. Calcd for $C_{17}H_{26}O_6FP$: C, 54.25; H, 6.96. Found: C, 54.17; H, 6.84%.

4.4. HWE reaction of triethyl 2-fluoro-2-phosphonoacetate (3) with 3-phenylpropionaldehyde (8b)

To a solution of phosphonoacetate **3** (201 μl, 0.99 mmol) in anhydrous THF (10 ml) was added a solution of *n*-BuLi (1.58 mol/l in *n*-hexane, 0.63 ml, 0.99 mmol) at 0 °C under argon. After being stirred at 0 °C for 1 h, 3-phenylpropionaldehyde (**8b**) (110 μl, 0.83 mmol) was slowly added to the solution at 0 °C. After being stirred at room temperature for 20 h, the reaction mixture was treated with 5% HCl (3 ml) and then extracted with AcOEt (20 ml×3). The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue (*E*:*Z*=92:8) was purified by silica gel column chromatography [*n*-hexane–AcOEt–acetone (100:4:1)] to afford a diastereomeric mixture of (*E*)-**7b** and (*Z*)-**7b** (142 mg, 77%) as a colorless oil.

4.4.1. Ethyl (*E*)-5-cyclopentyl-2-fluoro-2-pentenoate [(*E*)-7a]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01–1.16 (2H, m), 1.35 (3H, t, J=7.1 Hz), 1.39–1.69 (6H, m), 1.70–1.86 (3H, m), 2.52 (2H, q, J=7.8 Hz), 4.30 (2H, q, J=7.1 Hz), 5.94 (1H, dt, $^3J_{H,F}$=21.7 Hz, $^3J_{H,H}$=8.1 Hz); IR (neat) 1729, 1666, 1375, 1342, 1220, 1126 cm^{-1}; EIMS calcd for $C_{12}H_{19}FO_2$ MW 214.1369, found *m/z* 214.1349 (M^+).

4.4.2. Ethyl (*E*)-2-fluoro-5-phenyl-2-pentenoate [(*E*)-7b].[76] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, t, J=7.1 Hz), 2.70–2.93 (4H, m), 4.28 (2H, q, J=7.1 Hz), 5.93 (1H, dt, $^3J_{H,F}$=21.3 Hz, $^3J_{H,H}$=8.1 Hz), 7.15–7.40 (5H, m); IR (neat) 1730, 1455, 1375, 1261, 1024 cm^{-1}; EIMS calcd for $C_{13}H_{15}FO_2$ MW 222.1056, found *m/z* 222.1066 (M^+). Anal. Calcd for $C_{13}H_{15}FO_2$: C, 70.25; H, 6.80. Found: C, 70.08; H, 6.84%.

4.4.3. Ethyl (*E*)-3-cyclohexyl-2-fluoro-2-propenoate [(*E*)-7c].[30,77] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02–1.44 (9H, m), 1.60–1.82 (5H, m), 2.94–3.10 (1H, m), 4.29 (1H, q, J=7.2 Hz), 5.76 (1H, dd, $^3J_{H,F}$=22.0 Hz, $^3J_{H,H}$=10.3 Hz); IR (neat) 2929, 2852, 1729, 1300, 1213 cm^{-1}; EIMS calcd for $C_{11}H_{17}FO_2$ MW 200.1213, found *m/z* 200.1207 (M^+).

4.4.4. Ethyl (*E*)-2-fluoro-4,4-dimethyl-2-pentenoate [(*E*)-7d].[70] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (9H, s), 1.36 (3H, t, J=7.1 Hz), 4.30 (2H, q, J=7.1 Hz), 5.93 (1H, d, $^3J_{H,F}$=28.6 Hz); IR (neat) 1735, 1651, 1374, 1348, 1252 cm^{-1}; EIMS calcd for $C_9H_{15}FO_2$ MW 174.1056, found *m/z* 174.1030 (M^+).

4.4.5. Ethyl (*E*)-2-fluoro-3-phenyl-2-propenoate [(*E*)-7e].[26,71] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, t, J=7.1 Hz), 4.25 (2H, q, J=7.1 Hz), 6.92 (1H, d, $^3J_{H,F}$=22.2 Hz), 7.30–7.36 (3H, m), 7.44–7.47 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 61.6, 117.5 (d, $^2J_{C,F}$=25.5 Hz), 128.0, 128.7, 129.6 (d, $^4J_{C,F}$=2.5 Hz), 131.0 (d, $^3J_{C,F}$=9.3 Hz), 147.0 (d, $^1J_{C,F}$=255.3 Hz), 160.5 (d, $^2J_{C,F}$=36.7 Hz); IR (neat) 3058, 2983, 2939, 1732, 1656, 1494, 1448, 1375, 1284, 1230, 1132, 1022 cm^{-1}; ESIMS calcd for $C_{11}H_{11}NaFO_2$ MW 217.0641, found *m/z* 217.0657 (M^++Na).

4.4.6. Ethyl (*E*)-2-fluoro-3-(2-naphthyl)-2-propenoate [(*E*)-7f]. Colorless solid ($CHCl_3$–*n*-hexane), mp 32–34 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, t, J=7.1 Hz), 4.25 (2H, q, J=7.1 Hz), 7.07 (1H, d, $^3J_{H,F}$=22.2 Hz), 7.46–7.72 (3H, m), 7.77–7.90 (3H, m), 7.94 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 61.6, 121.6 (d, $^2J_{C,F}$=26.8 Hz), 126.3, 126.7, 127.1 (d, $^4J_{C,F}$=2.5 Hz), 127.5, 127.6, 128.2, 128.3, 128.4, 129.5 (d, $^4J_{C,F}$=3.7 Hz), 133.0 (d, $^3J_{C,F}$=23.7 Hz), 147.1 (d, $^1J_{C,F}$=255.3 Hz), 160.5 (d, $^2J_{C,F}$=36.1 Hz); IR (neat) 3056, 2983, 1730, 1651, 1506, 1468, 1375, 1336, 1226, 1132, 1020 cm^{-1}; ESIMS calcd for $C_{15}H_{14}FO_2$ MW 245.0978, found *m/z* 245.0970 (M^++H). Anal. Calcd for $C_{15}H_{13}FO_2$: C, 73.76; H, 5.36. Found: C, 73.45; H, 5.49%.

4.5. Synthesis of Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly (26)

4.5.1. Methyl 3-hydroxypropionate (16).[62] To a solution of sodium methoxide (146 mg, 2.65 mmol) in anhydrous MeOH (8 ml) was added β-propiolactone (**15**) (1.9 g, 26.5 mmol) at room temperature under argon. After being stirred at 50 °C for 4 h, the reaction mixture was submitted to filtration through a silica gel short column (Et_2O). The filtrate was concentrated in vacuo to afford **16** (2.74 g, quant.) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (1H, s, OH), 2.59 (2H, t, J=5.6 Hz), 3.72 (3H, s), 3.88 (2H, t, J=5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.6, 51.7, 58.2, 173.3.

4.5.2. Methyl 3-(*tert*-butyldiphenylsilyloxy)propanoate (17). To a solution of **16** (1.24 g, 11.9 mmol) in anhydrous CH_2Cl_2 (50 ml) were added imidazole (1.62 g, 23.8 mmol) and *tert*-butylchlorodiphenylsilane (3.1 ml, 11.9 mmol) at room temperature under argon. After being stirred at room temperature for 14 h, an aqueous solution saturated with NH_4Cl (20 ml) was added and then extracted with $CHCl_3$ (70 ml×3). The extract was dried over anhydrous $MgSO_4$,

filtered, and evaporated in vacuo to afford an oily residue, which was purified by chromatography on silica gel column [*n*-hexane–AcOEt (15:1)] to give **17** (3.92 g, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (9H, s), 2.58 (2H, t, J=6.3 Hz), 3.68 (3H, s), 3.94 (2H, t, J=6.3 Hz), 7.35–7.50 (6H, m), 7.62–7.74 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 26.7, 37.7, 51.5, 59.8, 127.7, 129.7, 133.5, 135.5, 172.1; IR (neat) 3072, 3049, 2931, 2858, 1745, 1589, 1471, 1429, 1362, 1194, 1111, 1008 cm^{-1}; ESIMS calcd for $C_{20}H_{27}O_3Si$ MW 343.1729, found *m*/*z* 343.1761 (M^++H). Anal. Calcd for $C_{20}H_{26}O_3Si$: C, 70.13; H, 7.65. Found: C, 69.72; H, 7.71%.

4.5.3. 3-(*tert*-Butyldiphenylsilyloxy)propanoic acid (18). To a solution of **17** (3.92 g, 11.4 mmol) in EtOH (15 ml) was added 1 N NaOH (11.4 ml), and the resulting mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated in vacuo, acidified with 10% HCl, and then extracted with $CHCl_3$ (50 ml×3). The extract was dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to afford **18** (3.74 g, 99%) as a white powder. Mp 95–97 °C ($CHCl_3$–*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 2.60 (2H, t, J=6.3 Hz), 3.95 (2H, t, J=6.3 Hz), 7.35–7.51 (6H, m), 7.63–7.75 (4H, m), 10.18–11.51 (1H, br s, CO_2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 26.7, 37.6, 59.5, 127.7, 129.7, 133.3, 135.5, 178.3; IR (KBr) 3261, 3070, 2929, 2858, 1587, 1469, 1427, 1390, 1109, 1045, 1008 cm^{-1}; ESIMS calcd for $C_{19}H_{24}NaO_3Si$ MW 351.1392, found *m*/*z* 351.1392 (M^++Na). Anal. Calcd for $C_{19}H_{24}O_3Si$: C, 69.47; H, 7.36. Found: C, 69.36; H, 7.65%.

4.5.4. 3-(*tert*-Butyldiphenylsilyloxy)propanoyl chloride (19). Oxalyl chloride (2.1 ml, 24.4 mmol) was added to a solution of **18** (4.0 g, 12.2 mmol) in anhydrous CH_2Cl_2 (50 ml) under argon. After being stirred at room temperature for 15 h, the reaction mixture was evaporated to dryness in vacuo to afford **19** (4.22 g, quant.) as a white powder, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 3.07 (2H, t, J=5.9 Hz), 3.96 (2H, t, J=5.9 Hz), 7.33–7.51 (6H, m), 7.63–7.75 (4H, m); IR (KBr) 3072, 2931, 2886, 2857, 1793, 1471, 1427, 1390, 1361, 1110 cm^{-1}; ESIMS calcd for $C_{19}H_{24}ClO_2Si$ MW 347.1234, found *m*/*z* 347.1240 (M^++H).

4.5.5. Ethyl (*Z*)-5-(*tert*-butyldiphenylsilyloxy)-2-fluoropent-2-enoate (21). A 1.6 mol/l solution of *n*-BuLi (7.6 ml, 12.2 mmol) in *n*-hexane was added to a stirred solution of phosphonoacetate **3** (2.4 ml, 11.6 mmol) in anhydrous THF (30 ml) at −78 °C under argon. The mixture was stirred at −78 °C for 1 h, and then a solution of acyl chloride **19** (4.22 g, 12.2 mmol) in anhydrous THF (30 ml) was added to the solution. After being stirred at −78 °C for 1 h, the reaction mixture was treated with 5% HCl (40 ml) and then extracted with $CHCl_3$ (100 ml×3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give an oily residue.

To a solution of the crude **20** in EtOH (30 ml) was added a solution of $NaBH_4$ (439 mg, 11.6 mmol) in EtOH (30 ml) at −78 °C under argon. After stirring at −78 °C for 2 h, the reaction mixture was allowed to warm to room temperature and then was stirred for 1 h. The mixture was treated with an aqueous solution saturated with NH_4Cl (50 ml), concentrated in vacuo, and then extracted with $CHCl_3$ (100 ml×3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue (*E*:*Z*=0:100) was purified by silica gel column chromatography [*n*-hexane–AcOEt (15:1)] to afford **21** (2.94 mg, 63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.33 (3H, t, J=7.1 Hz), 2.45–2.54 (2H, m), 3.74 (2H, t, J=6.4 Hz), 4.28 (2H, q, J=7.1 Hz), 6.23 (1H, dt, $^3J_{H,F}$=33.4 Hz, $^3J_{H,H}$=7.6 Hz), 7.33–7.49 (6H, m), 7.62–7.71 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.2, 26.8, 27.8 (d, $^3J_{C,F}$=2.5 Hz), 61.5, 62.1 (d, $^4J_{C,F}$=2.5 Hz), 117.5 (d, $^2J_{C,F}$=11.8 Hz), 127.7, 129.7, 133.5, 135.5, 148.7 (d, $^1J_{C,F}$=256.0 Hz), 160.7 (d, $^2J_{C,F}$=36.1 Hz); IR (neat) 3072, 2931, 1732, 1682, 1589, 1471, 1427, 1371, 1313, 1111 cm^{-1}; ESIMS calcd for $C_{23}H_{29}FNaO_3Si$ MW 423.1768, found *m*/*z* 423.1748 (M^++Na). Anal. Calcd for $C_{23}H_{29}FO_3Si$: C, 68.97; H, 7.30. Found: C, 68.67; H, 7.46%.

The geometry and the diastereomeric ratio of **21** were confirmed on the basis of the coupling constant between fluorine and the adjacent olefinic proton ($^3J_{H,F}$=33.4 Hz), and the integration of appropriate proton absorptions was obtained by ^{1}H NMR (400 MHz) analysis. The corresponding *E*-isomer of **21** was prepared by HWE reaction of phosphonoacetate **3** and 3-(*tert*-butyldiphenylsilyloxy)propanal[78,79] utilizing *n*-BuLi as a colorless oil. *E*-Isomer of **21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.33 (3H, t, J=7.1 Hz), 2.73–2.82 (2H, m), 3.74 (2H, t, J=6.1 Hz), 4.28 (2H, q, J=7.1 Hz), 6.05 (1H, dt, $^3J_{H,F}$=21.2 Hz, $^3J_{H,H}$=7.8 Hz), 7.33–7.48 (6H, m), 7.62–7.68 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.2, 26.8, 29.0 (d, $^3J_{C,F}$=5.0 Hz), 61.3, 62.7 (d, $^4J_{C,F}$=2.5 Hz), 120.5 (d, $^2J_{C,F}$=19.3 Hz), 127.7, 129.7, 133.5, 135.5, 147.7 (d, $^1J_{C,F}$=251.6 Hz), 160.9 (d, $^2J_{C,F}$=36.1 Hz); IR (neat) 3072, 2931, 2858, 1732, 1427, 1375, 1325, 1217, 1111 cm^{-1}; ESIMS calcd for $C_{23}H_{29}FNaO_3Si$ MW 423.1768, found *m*/*z* 423.1800 (M^++Na). Anal. Calcd for $C_{23}H_{29}FO_3Si$: C, 68.97; H, 7.30. Found: C, 68.80; H, 7.29%.

4.5.6. (*Z*)-5-(*tert*-Butyldiphenylsilyloxy)-2-fluoropent-2-en-1-ol (22). To a solution of **21** (458 mg, 1.14 mmol) in anhydrous THF (10 ml) was added $LiAlH_4$ (91 mg, 2.4 mmol) at 0 °C under argon. After being stirred at 0 °C for 30 min, the reaction mixture was treated with 5% HCl (10 ml) and then extracted with $CHCl_3$ (50 ml×3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by silica gel column chromatography [*n*-hexane–AcOEt (4:1)] to afford **22** (380 mg, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 2.28–2.43 (2H, m), 3.69 (2H, t, J=6.6 Hz), 4.08 (2H, dd, $^3J_{H,F}$=15.6 Hz, $^3J_{H,H}$=6.4 Hz), 4.90 (1H, dt, $^3J_{H,F}$=36.9 Hz, $^3J_{H,H}$=7.6 Hz), 7.32–7.48 (6H, m), 7.57–7.72 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.8, 27.0 (d, $^3J_{C,F}$=3.7 Hz), 61.4 (d, $^2J_{C,F}$=32.4 Hz), 63.0 (d, $^4J_{C,F}$=1.9 Hz), 104.6 (d, $^2J_{C,F}$=13.7 Hz), 127.6, 129.6, 133.8, 135.6, 158.4 (d, $^1J_{C,F}$=255.4 Hz); IR (neat) 3356, 3072, 2931, 2858, 1714, 1589, 1471, 1427, 1390, 1111, 1020 cm^{-1}; ESIMS calcd for $C_{21}H_{28}FO_2Si$ MW 359.1843, found *m*/*z* 359.1879 (M^++H). Anal. Calcd for $C_{21}H_{27}FO_2Si$: C, 70.35; H, 7.59. Found: C, 70.06; H, 7.39%.

4.5.7. Benzyl (*Z*)-5-(*tert*-butyldiphenylsilyloxy)-2-fluoropent-2-enylcarbamate (24). To a solution of **22** (500 mg, 1.40 mmol) in anhydrous CH_2Cl_2 (15 ml) were added

PPh_3 (475 mg, 1.81 mmol) and *N*-Cbz-NsNH (610 mg, 1.81 mmol), and then a 2.2 mol/l solution of DEAD (823 μl, 1.81 mmol) in toluene was added slowly at room temperature under argon. After being stirred at room temperature for 1 h, the reaction mixture was concentrated in vacuo. The crude solid was purified by silica gel column chromatography [*n*-hexane–AcOEt (4:1)] to afford crude **23** (1.03 g) as a yellow oil, which was used without further purification.

To a solution of **23** (360 mg) in anhydrous DMF (3 ml) were added K_2CO_3 (220 mg, 1.60 mmol) and 4-*tert*-butylthiophenol (116 μl, 0.69 mmol) at room temperature under argon. After being stirred at room temperature for 15 min, the reaction mixture was treated with 5% HCl (10 ml) and then extracted with $CHCl_3$ (20 ml×3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by silica gel column chromatography [*n*-hexane–AcOEt (7:1)] to afford **24** (230 mg, 95%) as a colorless solid. Mp 44–45 °C ($CHCl_3$–*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 2.16–2.52 (2H, m), 3.66 (2H, t, J=6.6 Hz), 3.86 (2H, dd, $^3J_{H,F}$=14.9 Hz, $^3J_{H,H}$=5.9 Hz), 4.68–4.97 (2H, m, olefinic proton and NH), 5.11 (2H, s), 7.28–7.53 (11H, m), 7.61–7.69 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.8, 27.0 (d, $^3J_{C,F}$=3.7 Hz), 41.7 (d, $^2J_{C,F}$=31.8 Hz), 62.9 (d, $^4J_{C,F}$=2.5 Hz), 66.9, 104.2 (d, $^2J_{C,F}$=13.7 Hz), 127.6, 128.08, 128.11, 128.5, 129.6, 133.7, 135.5, 136.3, 156.10, 156.12 (d, $^1J_{C,F}$=255.4 Hz); IR (neat) 3334, 3070, 2931, 2858, 1714, 1518, 1427, 1390, 1250, 1111 cm^{-1}; ESIMS calcd for $C_{29}H_{35}FNO_3Si$ MW 492.2383, found *m/z* 492.2370 (M^++H). Anal. Calcd for $C_{29}H_{34}FNO_3Si$: C, 70.84; H, 6.97; N, 2.85. Found: C, 70.61; H, 6.98; N, 2.81%.

4.5.8. Benzyl (*Z*)-2-fluoro-5-hydroxypent-2-enylcarbamate (25). A 1.0 mol/l solution of TBAF (927 μl, 0.927 mmol) in THF was added to a stirred solution of **24** (380 mg, 0.77 mmol) in anhydrous THF (20 ml) at room temperature under argon. The mixture was stirred at room temperature for 45 min, after which the reaction mixture was treated with an aqueous solution saturated with $NaHCO_3$ (10 ml) and then extracted with $CHCl_3$ (30 ml×3). The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by silica gel column chromatography [*n*-hexane–AcOEt (1:1)] to afford **25** (180 mg, 92%) as a white powder. Mp 55–57 °C ($CHCl_3$–*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (1H, br s, OH), 2.29–2.41 (2H, m), 3.65 (2H, t, J=6.1 Hz), 3.90 (2H, dd, $^3J_{H,F}$=14.4 Hz, $^3J_{H,H}$= 6.1 Hz), 4.86 (1H, dt, $^3J_{H,F}$=36.4 Hz, $^3J_{H,H}$=7.3 Hz), 4.95–5.06 (1H, br s, NH), 5.12 (2H, s), 7.29–7.46 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0 (d, $^3J_{C,F}$=3.7 Hz), 41.7 (d, $^3J_{C,F}$=10.0 Hz), 61.5, 67.0, 104.0 (d, $^2J_{C,F}$=13.7 Hz), 128.1, 128.2, 128.5, 136.2, 156.4, 156.6 (d, $^1J_{C,F}$=255.4 Hz); IR (KBr) 3319, 3064, 2945, 1712, 1687, 1547, 1454, 1259, 1138, 1051 cm^{-1}; ESIMS calcd for $C_{13}H_{16}FNNaO_3$ MW 276.1012, found *m/z* 276.1016 (M^++Na). Anal. Calcd for $C_{13}H_{16}FNO_3$: C, 61.65; H, 6.37; N, 5.53. Found: C, 61.42; H, 6.26; N, 5.49%.

4.5.9. (*Z*)-5-(Benzyloxycarbonylamino)-4-fluoropent-3-enoic acid {Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly, 26}. To a solution of **25** (100 mg, 0.395 mmol) in acetone (5 ml) was added Jones reagent (500 μl) at 0 °C. After the reaction mixture was stirred at room temperature for 30 min, 2-propanol (1 ml) was added to it and the resulting mixture was then stirred until the color of the reaction mixture disappeared. After filtration, the filtrate was concentrated in vacuo and then treated with an aqueous solution saturated with $NaHCO_3$ (20 ml), washed with $CHCl_3$ (20 ml). The aqueous layer was acidified with 10% HCl (10 ml) and then extracted with AcOEt (50 ml×5). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford **26** (85 mg, 80%) as a white powder. Mp 74–75 °C ($CHCl_3$–*n*-hexane); ^{1}H NMR (400 MHz, DMSO) δ 3.02 (2H, d, J=7.1 Hz), 3.25–3.43 (1H, br s, NH), 3.76 (2H, dd, $^3J_{H,F}$=12.7 Hz, $^3J_{H,H}$=5.9 Hz), 4.90–5.09 (3H, m), 7.26–7.45 (5H, m), 12.16–12.63 (1H, br s, CO_2H); ^{13}C NMR (75 MHz, CD_3OD) δ 29.7 (d, $^3J_{C,F}$=5.6 Hz), 42.0 (d, $^2J_{C,F}$=33.6 Hz), 67.7, 100.6 (d, $^2J_{C,F}$=12.5 Hz), 128.8, 129.0, 129.5, 138.2, 158.7, 158.9 (d, $^1J_{C,F}$=257.2 Hz), 174.6; IR (KBr) 3313, 2956, 1687, 1550, 1271, 1167, 1140, 1053, 993 cm^{-1}; ESIMS calcd for $C_{13}H_{14}FNNaO_4$ MW 290.0805, found *m/z* 290.0821 (M^++Na). Anal. Calcd for $C_{13}H_{14}FNO_4$: C, 58.42; H, 5.28; N, 5.24. Found: C, 57.98; H, 5.42; N, 4.93%.

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References and notes

1. Normant, J. F.; Foulon, J. P.; Masure, D.; Sauvetre, R.; Villieras, J. *Synthesis* **1975**, 122–125.
2. Camps, F.; Coll, J.; Fabrias, G.; Guerrero, A. *Tetrahedron* **1984**, *40*, 2871–2878.
3. Coutrot, P.; Grison, C.; Sauvêtre, R. *J. Organomet. Chem.* **1987**, *332*, 1–8.
4. Ishihara, T.; Kuroboshi, M. *Chem. Lett.* **1987**, 1145–1148.
5. Allmendinger, T. *Tetrahedron* **1991**, *47*, 4905–4914.
6. Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641–1716 and references cited therein.
7. Sano, S.; Yokoyama, K.; Fukushima, M.; Yagi, T.; Nagao, Y. *Chem. Commun.* **1997**, 559–560.
8. Sano, S.; Ando, T.; Yokoyama, K.; Nagao, Y. *Synlett* **1998**, 777–779.
9. Sano, S. *Yakugaku Zasshi* **2000**, *120*, 432–444.
10. Sano, S.; Yokoyama, K.; Teranishi, R.; Shiro, M.; Nagao, Y. *Tetrahedron Lett.* **2002**, *43*, 281–284.
11. Sano, S.; Yokoyama, K.; Shiro, M.; Nagao, Y. *Chem. Pharm. Bull.* **2002**, *50*, 706–709.
12. Sano, S.; Takehisa, T.; Ogawa, S.; Yokoyama, K.; Nagao, Y. *Chem. Pharm. Bull.* **2002**, *50*, 1300–1302.
13. Sano, S.; Teranishi, R.; Nagao, Y. *Tetrahedron Lett.* **2002**, *43*, 9183–9186.
14. Sano, S.; Teranishi, R.; Nakano, F.; In, K.; Takeshige, H.; Ishii, T.; Shiro, M.; Nagao, Y. *Heterocycles* **2003**, *59*, 793–804.
15. Sano, S.; Takemoto, Y.; Nagao, Y. *ARKIVOC* **2003**, 93–101.
16. Sano, S.; Takemoto, Y.; Nagao, Y. *Tetrahedron Lett.* **2003**, *44*, 8853–8855.

17. Sano, S.; Kujime, E.; Takemoto, Y.; Shiro, M.; Nagao, Y. *Chem. Pharm. Bull.* **2005**, *53*, 131–134.
18. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
19. Ghosh, A. K.; Wang, Y.; Kim, J. T. *J. Org. Chem.* **2001**, *66*, 8973–8982.
20. Machleidt, H.; Wessendorf, R. *Justus Liebigs Ann. Chem.* **1964**, *674*, 1–10.
21. Liu, R. S. H.; Matsumoto, H.; Asato, A. E.; Denny, M.; Shichida, Y.; Yoshizawa, T.; Dahlquist, F. W. *J. Am. Chem. Soc.* **1981**, *103*, 7195–7201.
22. Lovely, A. J.; Pawson, B. A. *J. Med. Chem.* **1982**, *25*, 71–75.
23. Asato, A. E.; Kini, A.; Denny, M.; Liu, R. S. H. *J. Am. Chem. Soc.* **1983**, *105*, 2923–2924.
24. Etemad-Moghadam, G.; Seyden-Penne, J. *Bull. Soc. Chim. Fr.* **1985**, 448–454.
25. Collins, P. W.; Kramer, S. W.; Gullikson, G. W. *J. Med. Chem.* **1987**, *30*, 1952–1955.
26. Thenappan, A.; Burton, D. J. *J. Org. Chem.* **1990**, *55*, 4639–4642.
27. Tsai, H.-J.; Thenappan, A.; Burton, D. J. *Tetrahedron Lett.* **1992**, *33*, 6579–6582.
28. Patrick, T. B.; Lanahan, M. V.; Yang, C.; Walker, J. K.; Hutchinson, C. L.; Neal, B. E. *J. Org. Chem.* **1994**, *59*, 1210–1212.
29. Tsai, H.-J.; Thenappan, A.; Burton, D. J. *J. Org. Chem.* **1994**, *59*, 7085–7091.
30. Piva, O. *Synlett* **1994**, 729–731.
31. Shinada, T.; Sekiya, N.; Bojkova, N.; Yoshihara, K. *Synlett* **1995**, 1247–1248.
32. Shen, Y.; Ni, J. *J. Org. Chem.* **1997**, *62*, 7260–7262.
33. Sano, S.; Saito, K.; Nagao, Y. *Tetrahedron Lett.* **2003**, *44*, 3987–3990.
34. Allmendinger, T.; Furet, P.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7297–7300.
35. Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7301–7304.
36. Lin, J.; Toscano, P. J.; Welch, J. T. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 14020–14024.
37. Chevrie, D.; Lequeux, T.; Pommelet, J.-C. *Org. Lett.* **1999**, *1*, 1539–1541.
38. Welch, J. T.; Allmendinger, T. *Fluoroolefin Isosteres*; Kazmierski, W. M., Ed.; Methods in Molecular Medicine; Humana: Totowa, NJ, 1999; Vol. 23 (Peptidomimetics Protocols), pp 357–384.
39. Otaka, A.; Watanabe, H.; Mitsuyama, E.; Yukimasa, A.; Tamamura, H.; Fujii, N. *Tetrahedron Lett.* **2001**, *42*, 285–287.
40. Otaka, A.; Watanabe, H.; Yukimasa, A.; Oishi, S.; Tamamura, H.; Fujii, N. *Tetrahedron Lett.* **2001**, *42*, 5443–5446.
41. Okada, M.; Nakamura, Y.; Saito, A.; Sato, A.; Horikawa, H.; Taguchi, T. *Tetrahedron Lett.* **2002**, *43*, 5845–5847.
42. Hata, H.; Kobayashi, T.; Amii, H.; Uneyama, K.; Welch, J. T. *Tetrahedron Lett.* **2002**, *43*, 6099–6102.
43. Chevrie, D.; Lequeux, T.; Pommelet, J.-C. *Tetrahedron* **2002**, *58*, 4759–4767.
44. Zhao, K.; Lim, D. S.; Funaki, T.; Welch, J. T. *Bioorg. Med. Chem.* **2003**, *11*, 207–215.
45. Otaka, A.; Mitsuyama, E.; Watanabe, J.; Watanabe, H.; Fujii, N. *Biopolymers* **2004**, *76*, 140–149.
46. Otaka, A.; Watanabe, J.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2004**, *69*, 1634–1645.
47. Nakamura, Y.; Okada, M.; Sato, A.; Horikawa, H.; Koura, M.; Saito, A.; Taguchi, T. *Tetrahedron* **2005**, *61*, 5741–5753.
48. Nakamura, Y.; Okada, M.; Koura, M.; Tojo, M.; Saito, A.; Sato, A.; Taguchi, T. *J. Fluorine Chem.* **2006**, *127*, 627–636.
49. Niida, A.; Mizumoto, M.; Narumi, T.; Inokuchi, E.; Oishi, S.; Ohno, H.; Otaka, A.; Kitaura, K.; Fujii, N. *J. Org. Chem.* **2006**, *71*, 4118–4129.
50. Pascual, C.; Meier, J.; Simon, W. *Helv. Chim. Acta* **1966**, *49*, 164–168.
51. Tobey, S. W. *J. Org. Chem.* **1969**, *34*, 1281–1298.
52. Matter, U. E.; Pascual, C.; Pretsch, E.; Pross, A.; Simon, W.; Sternhell, S. *Tetrahedron* **1969**, *25*, 691–697.
53. Thenappan, A.; Burton, D. J. *J. Org. Chem.* **1991**, *56*, 273–277.
54. Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199–2204.
55. Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61–70.
56. Chérest, M.; Prudent, N. *Tetrahedron* **1980**, *36*, 1599–1606.
57. Wu, Y. D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 906–908.
58. Wu, Y. D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908–910.
59. Wu, Y. D.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5560–5561.
60. Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456–458.
61. Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VCH: New York, NY, 1991; pp 47–60.
62. Hollowood, C. J.; Yamanoi, S.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 1664–1665.
63. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.
64. Fukuyama, T.; Cheung, M.; Kan, T. *Synlett* **1999**, 1301–1303.
65. Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353–359.
66. Barma, D. K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 3218–3219.
67. Yoshimatsu, M.; Murase, Y.; Itoh, A.; Tanabe, G.; Muraoka, O. *Chem. Lett.* **2005**, *34*, 998–999.
68. Suzuki, Y.; Sato, M. *Tetrahedron Lett.* **2004**, *45*, 1679–1681.
69. Elkik, E.; Imbeaux-Oudotte, M. *Tetrahedron Lett.* **1985**, *26*, 3977–3980.
70. Abraham, R. J.; Ellison, S. L. R.; Barfield, M.; Thomas, W. A. *J. Chem. Soc., Perkin Trans. 2* **1987**, 977–985.
71. Miyake, N.; Kitazume, T. *J. Fluorine Chem.* **2003**, *122*, 243–246.
72. List, B.; Doehring, A.; Fonseca, M. T. H.; Job, A.; Torres, R. R. *Tetrahedron* **2006**, *62*, 476–482.
73. Reiter, M.; Turner, H.; Mills-Webb, R.; Gouverneur, V. *J. Org. Chem.* **2005**, *70*, 8478–8485.
74. Snider, B. B.; Kiselgof, J. Y. *Tetrahedron* **1998**, *54*, 10641–10648.
75. Gomez-Monterrey, I.; Turcaud, S.; Lucas, E.; Bruetschy, L.; Roques, B. P.; Fournie-Zaluski, M. C. *J. Med. Chem.* **1993**, *36*, 87–94.
76. Morikawa, T.; Sasaki, H.; Mori, K.; Shiro, M.; Taguchi, T. *Chem. Pharm. Bull.* **1992**, *40*, 3189–3193.
77. Bargiggia, F.; Dos Santos, S.; Piva, O. *Synthesis* **2002**, 427–437.
78. Fréchet, J. M. J.; Warnock, J.; Farrall, M. J. *J. Org. Chem.* **1978**, *43*, 2618–2621.
79. Miranda, P. O.; Estévez, F.; Quintana, J.; García, C. I.; Brouard, I.; Padrón, J. I.; Pivel, J. P.; Bermejo, J. *J. Med. Chem.* **2004**, *47*, 292–295.