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Copper mediated defluorinative allylic alkylation of difluorohomoallyl alcohol derivatives directed to an efficient synthetic method for (*Z*)-fluoroalkene dipeptide isosteres

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ABSTRACT

Difluoroallylation of optically pure *O*-silylated (*S*)-2-methyl-3-hydroxypropanal **10a** with bromodifluoropropene mediated by indium provided the corresponding difluorohomoallyl alcohol **11a** with low diastereoselectivity, but without a decrease in optical purity. Defluorinative allylic alkylation of each diastereomer of the difluorohomoallyl alcohol efficiently proceeded by the reaction with trialkylaluminium and Cu(I) system or Grignard reagent and a catalytic amount of CuI system in THF to give the fluorine-substituted allylic alcohol **12** in an high yield and in an excellent *Z* selective manner. Subsequent imidate Claisen rearrangement of the allylic alcohol **12** proceeded with a complete 1,3-chirality transfer to give the fluoroalkene dipeptide isostere structure **14** after the final conversion of the primary alcohol **20** into the carboxylic acid form.

1. Introduction

It has been widely accepted that a fluoroalkene moiety (–CF = CH–) would be an ideal mimic for an amide bond (–CO–NH–) due to the similarity of both steric and electronic properties. Contrary to such similarities, fluoroalkene moiety would be a nonhydrolyzable bond both chemically and enzymatically, and the lack of rotational freedom of this bond is also a different property from that of an amide bond [1]. Due to these unique properties, utilization of fluoroalkene dipeptide isosteres as nonhydrolyzable and/or conformationally restricted replacements for the parent amide bonds has attracted much attention in the field of medicinal chemistry [2,3]. Not only such an application of fluoroalkene compounds in medicinal chemistry [2–4], but also functionalized fluoroalkene compounds are important in synthetic chemistry as a building block for a variety type of organofluorine compounds [5].

For the synthesis of such fluoroalkene dipeptide isosteres, stereo-control of the C–C double bond configuration (either *Z* or *E*) and the relative stereochemistry of the two chiral centers at C2 and C5 (either *syn* or *anti*) is a major issue to be solved (see, Fig. 1). In addition to these, final product should be prepared in optically pure form. Although, so far, a number of reports dealing with the preparative methods for such compounds have been appeared [2,6–13], till now development of more convenient methods is a current subject.

We have reported a highly regio- and stereoselective route involving defluorinative allylic alkylation of 5-hydroxy-4,4-difluoro-2-alken-1-ol **1** with a trialkylaluminium-Cu(I) system to introduce an alkyl group into 2 position in an excellent 2,5-*syn* and *Z* selective manner giving rise to the fluoro-olefin compound **2**. Subsequent conversion of the hydroxy group into the amino group via S_N2 azidation step of **3** with NaN_3 via unstable mesylate followed by immediate $LiAlH_4$ reduction of the azide **4** gave the *N*-protected amino alcohol **5** (Scheme 1) [13a,b].

Although our method proceeds in a highly stereo-controlled manner, it has some disadvantages to be solved. (1) Firstly, availability of trialkylalminium is quite limited. (2) In this reaction, due to relatively low reactivity, an excess amount of trialkyaluminium (5 molar equivalent under optimized conditions) and copper salt (2.5 equivalent) as well as long reaction time are required. In particular, compared to the *E* isomer, the *Z* isomer of the starting material (***Z***) – **1** showed much lower reactivity to give the desired product ***anti*-2** in low yield. (3) Although in a laboratory

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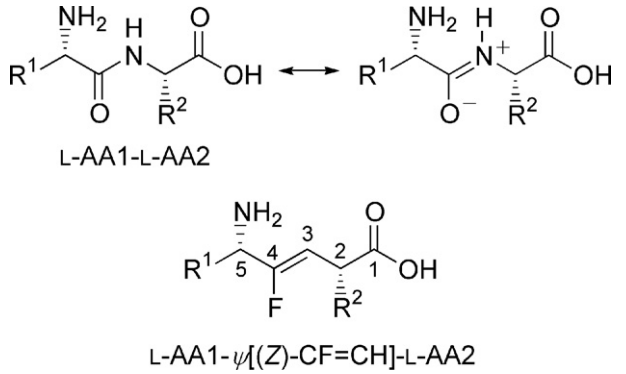


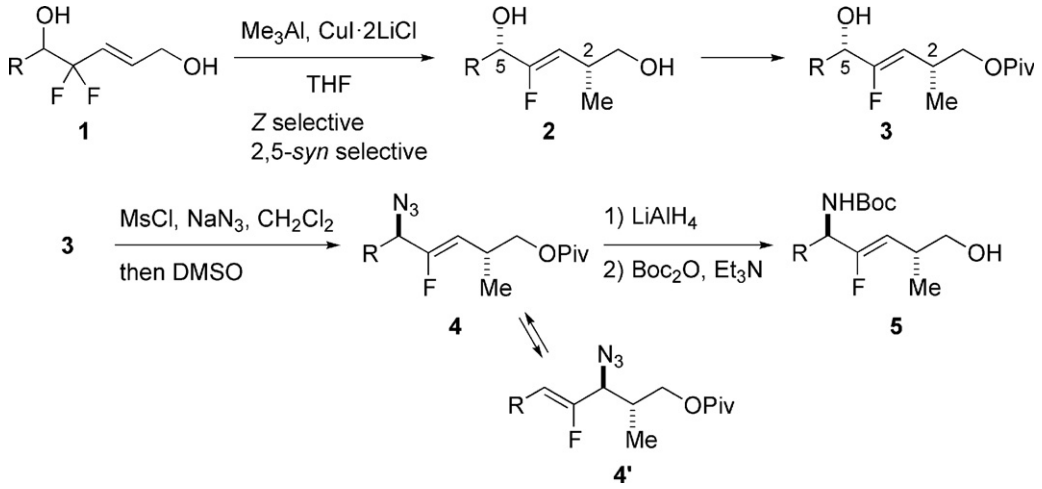
Fig. 1. Natural dipeptide and its fluoroalkene isostere.

experimental work a variety of Grignard reagents can be available or can be easily prepared, Grignard reagent did not work well with this starting material **1** having a vicinally disubstituted olefin structure, instead giving rise to a complex mixture. (4) Conversion of the allylic hydroxy group in the alkylated product **2** into the amino group via the azide intermediate **4** is somewhat problematic, since [3,3]-sigmatropic rearrangement of the allylic azide **4** easily proceeds to give a mixture of the regio isomers (**4** + **4**′) (Scheme 1) [13b,14]. (5) *Syn* selective conversion of **(*E*)** – **1** into **2** and S_N2 type azidation provides a fluoroalkene dipeptide isostere corresponding to the L-AA1-D-AA2 or D-AA1-L-AA2 dipeptide form containing unnatural D form amino acid. (6) Improvement for the preparation of the starting material **1** is also a remaining subject. That is, multiple steps are required for the preparation of **1** [13]. Furthermore, we need convenient procedures to obtain both enantiomers of **1** in optically pure form.

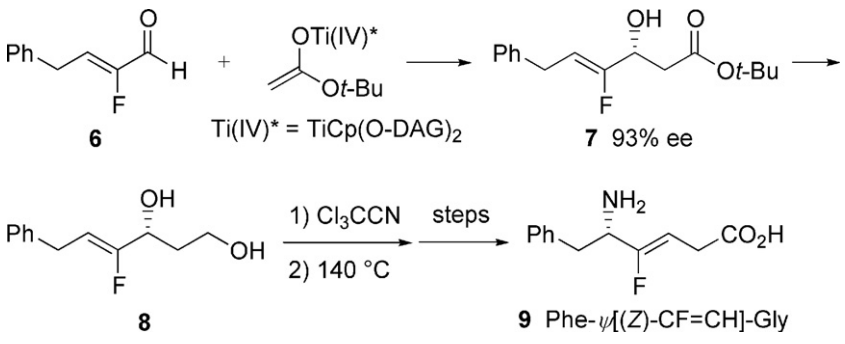
Considering above mentioned issues, an alternative starting material should be chosen mainly on the basis of its reactivity in the reaction with readily available organometallics such as Grignard reagent and its easy availability in optically pure form. Furthermore, the use of problematic allylic azide intermediate should be avoided.

In Allemendinger's pioneering synthetic work for the preparation of fluoroalkene dipeptide isosteres such as Phe–ψ[(*Z*)–CF = CH]–Gly **9**, *Z* configuration of the C–C double bond was derived by the use of a *Z* isomer of α-fluoro-α,β-unsaturated aldehyde **6** as a starting material and the stereo-control of the configuration of the amino functionality was achieved by chirality transfer through the imidate Claisen rearrangement (Overman rearrangement) of the chiral fluorinated allylic alcohol **8** obtained by enantioselective aldol reaction of the aldehyde **6** with chiral titanium enolate (Scheme 2) [6]. Later similar strategies were also reported by other groups [7]. Although the enatioselective or diastereoselective aldol reaction is not always a facile route to obtain the product such as **7** in completely optically pure form, an excellent chirality transfer and operational simplicity of the latter rearrangement attracted our interest.

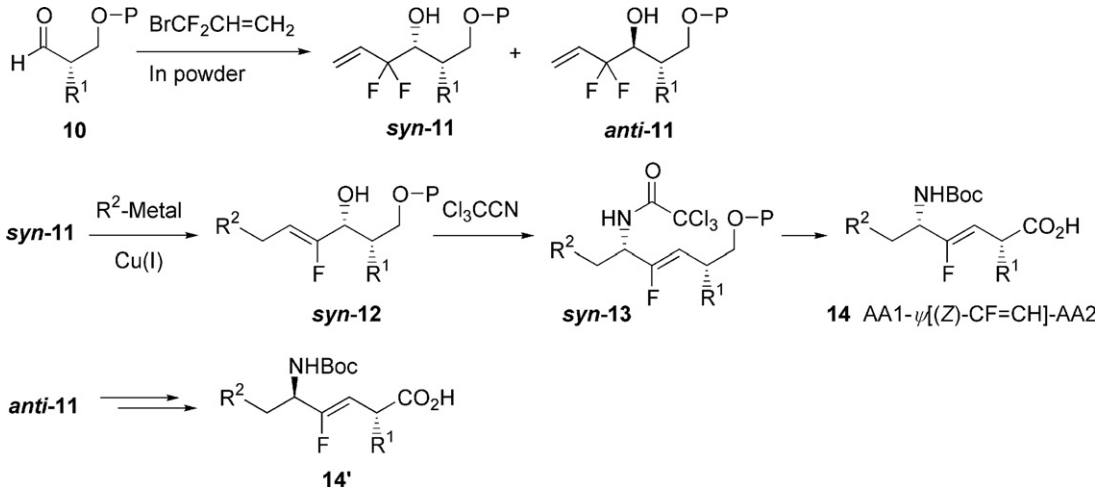
In Scheme 3 is depicted our second route for the preparation of AA1–ψ[(*Z*)–CF = CH]–AA2 **14**, where the corresponding dipeptide is consisting of two amino acids AA1 and AA2. In this scheme difluoroallylation of the chiral aldehyde **10** (P = protective group) with bromodifluoropropene provided a diastereomer mixture of the alcohol **11** easily separated by column chromatography. Subsequently, copper mediated defluorinative allylic alkylation of diastereomerically pure **11** with organometallics (trialkylalu-



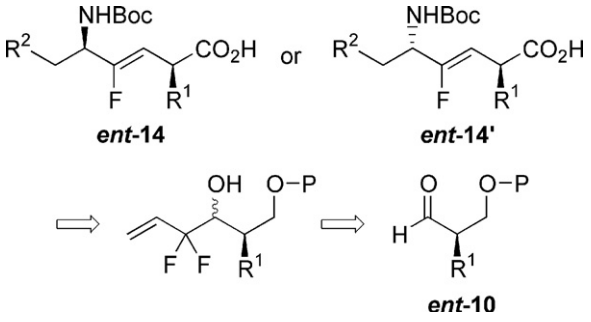
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

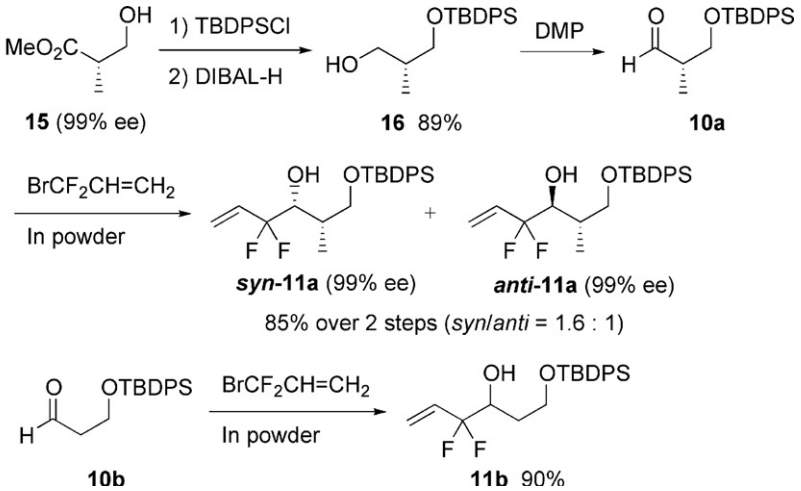
minium, Grignard reagent or alkyllithium) was examined to optimize the reaction conditions leading to the desired product **12** in high yield and in an excellent *Z* selective manner. The imidate Claisen rearrangement of **12** proceeded nicely, as expected, to give the amide compound **13**, which was finally converted to the corresponding fluoroalkene dipeptide isostere **14**. As easily expected from Scheme 3, by using ***anti*-11** the dipeptide isostere having opposite configuration of the amino group **14′** can be synthesized.

Furthermore, the corresponding enantiomers ***ent*-14** and ***ent*-14′** can be prepared by the use of the enantiomer of the starting aldehyde ***ent*-10** (Scheme 4). For the preparation of the starting aldehyde **10** or ***ent*-10** in optically pure form, we can use commercially available precursors although very limited with respect to alkyl substituent (R^1 in **10**) [15]. As described in this paper we used commercially available hydroxy ester **15** (>99% ee) as a substitute of L-Ala moiety (see Scheme 5). Alternatively, as one of the general methods, diastereoselective aldolization of chiral enolate having an appropriate chiral auxiliary with formaldehyde [8,16] or desymmetrization of σ-symmetric 2-substituted propane-1,3-diols or their derivatives such as diesters [17] would be promising procedures.

In this paper we describe a full detail of our method, in particular the chemistry of copper mediated defluorinative allylic alkylation of the difluorovinyl compound **11** with trialkylaluminium, Grignard reagent or alkyllithium.

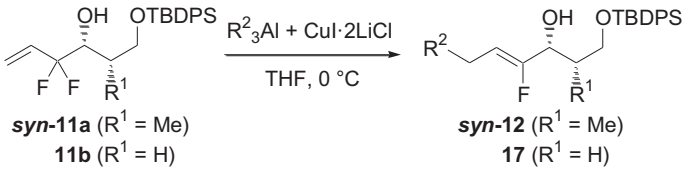
2. Results and discussion

According to the reported procedure, difluorohomoallyl alcohol **11** was prepared in good yield by indium-mediated difluoroallylation of the aldehyde with bromodifluoropropene (Scheme 5) [18,19]. In the case of α-methylated chiral aldehyde **10a** [20] derived from the commercially available ester **15** (purity: 99% ee) allylation reaction proceeded smoothly to give a diastereomer mixture (**11a**, 85% yield, *syn*/*anti* = 1.6:1), which was easily separated by column chromatography on silica gel. Optical purity of the each isomer was found to be 99% ee keeping that of the starting material when the intermediate aldehyde **10a** was used



Scheme 5.

Table 1
Defluorinative allylic alkylation of ***syn*-11a** and **11b** with R_3Al + Cu(I) system.



***syn*-11a** (R^1 = Me)
11b (R^1 = H)
***syn*-12** (R^1 = Me)
17 (R^1 = H)

Entry	11	$R^2{}_3Al$ (equiv)	CuI·2LiCl (equiv)	Time (h)	Product	Yield[a] (%)	*Z*/*E*[b]
1	***syn*-11a**	Me_3Al (5.0)	2.5	18	***syn*-12a**	92	>19:1
2	***syn*-11a**	Me_3Al (5.0)	0	23	***syn*-12a**	0[c]	
3	***syn*-11a**	Ph_3Al[d] (5.0)	2.5	24	***syn*-12b**	22	5:1
4	***syn*-11a**	Ph_3Al[e] (5.0)	2.5	18	***syn*-12b**	85	14:1
5	**11b**[f]	Me_3Al (5.0)	2.5	23	**17a**	97	>19:1
6	**11b**[f]	i-Bu_3Al (5.0)	2.5	48	**17c**	84	17:1

[a] Isolated yield.
[b] Ratio was determined by 300 MHz ^1H NMR of the crude mixture.
[c] Recovery of the starting material ***syn*-11a**.
[d] Ph_3Al was preparated by the reaction of PhLi and $AlCl_3$.
[e] Ph_3Al was preparated by the reaction of PhMgBr and $AlCl_3$.
[f] **11b** was racemic form.

without purification by column chromatography after oxidation of the monoprotected diol **16** with Dess-Martin periodinane [21].

2.1. Copper mediated allylic alkylation reaction

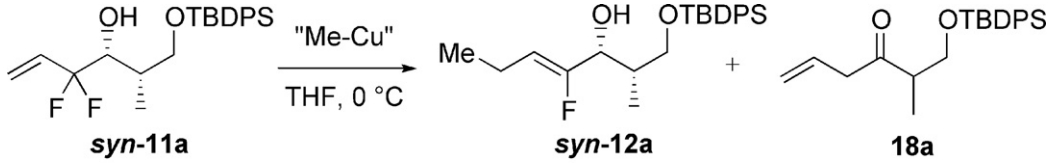
As shown in Scheme 1, we reported that defluorinative allylic alkylation of the difluorohomoallyl alcohol derivative **1** having a vicinally disubstituted olefin structure efficiently proceeded by treating with trialkylaluminium (Me_3Al and *i*-Bu_3Al) and CuI·2LiCl in THF [22,23] to give **2** in an excellent *Z* and 2,5-*syn* selective manner [13]. Therefore, at first similar procedure was conducted using the vinyl type substrate **11**. Results obtained with ***syn*-11a** and **11b** are summarized in Table 1.

While in the absence of CuI·2LiCl trimethylaluminium did not react with the difluorohomoallyl compound ***syn*-11a** in THF resulting in the recovery of the starting material, the desired methylated product ***syn*-12a** was obtained in excellent yield (92%) with *Z* selective manner by treating with a combination of Me_3Al (5 equiv) and CuI·2LiCl (2.5 equiv) in THF for 18 h (entries 1, 2). Similar result was obtained in the reaction of Me_3Al with racemic **11b** (**17a**, 97% yield, *Z*/*E* = >19:1, entry 5). Compared with Me_3Al, the longer alkyl isobutyl derivative (*i*-Bu_3Al, commercially available, hexane solution) showed lower reactivity to give the product **17c** in 84% yield with high *Z* selectivity (*Z*/*E* = 17:1) after the reaction for 48 h (entry 6 vs entries 1, 5). Since triphenylaluminiun (Ph_3Al) was not commercially available, we used Ph_3Al in situ generated from the reaction of phenyllithium or phenylmagnesium bromide (both commercially available, diethyl ether solution) with $AlCl_3$ in THF (entries 3, 4) and we found different reactivity in the present reaction. That is, while the use of Ph_3Al derived from phenyllithium resulted in low yield and low stereoselectivity (***syn*-12b**, 22% yield, *Z*/*E* = 5.0: 1, entry 4), the use of PhMgBr/$AlCl_3$ in the presence of CuI·2LiCl gave the desired product in reasonable yield with high *Z* selectivity (***syn*-12b**, 85% yield, *Z*/*E* = 14:1, entry 5).

Similar tendency (low stereoselectivity and by-product formation) when using a copper reagent derived from organolithium was also observed as in the case of the Gilman reagent. As shown in Scheme 6, reaction of ***syn*-11a** with the Gilman reagent Me_2CuLi prepared from MeLi (Et_2O solution) and CuI in THF at 0 °C gave the methylated product ***syn*-12a** in 81% yield with low selectivity (*Z*/*E* = 5.1:1) along with the formation of the defluorinated ketone compound **18a** as a by-product in 13% yield, which was not found out in the copper mediated reaction with Me_3Al or MeMgBr. Similarly, reaction of **11b** with Me_2CuLi gave the methylated product **17a** in 64% yield (*Z*/*E* = 5.0:1) accompanying the formation of the defuorinated ketone **18b** (demethylated compound of **18a**) in 20% yield.

Although mechanistic detail for the formation of **18** is not clear, reductive defluorination of α-fluoroketone compound A by Me_2CuLi would be one of the possible pathways, since several similar vinylogous reactions using cuprates [11a,13d,24] and reductive defluorination of α-fluorinated ketones by low valent metals [25,26] were reported to proceed via initial single electron transfer (SET) to enoate or carbonyl π-system. The requisite α-fluoroketone compound A would be formally formed by dehydrofluorination of **11** due to the highly basic media in the case of Me_2CuLi as compared to Grignard reagent or alkylalminium (Scheme 7).

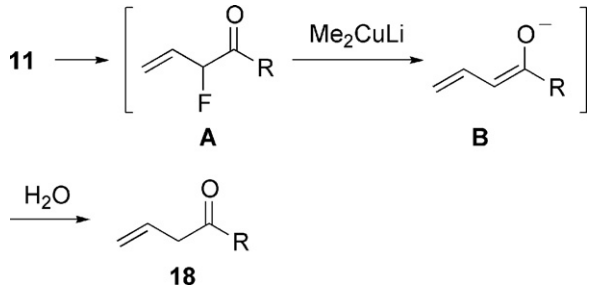
As described above, the use of organoaluminium or organolithium reagent for the copper mediated allylic alkylation of



***syn*-11a** ***syn*-12a** **18a**

Me_2CuLi (2.5)	6 h	81% (*Z*/*E* = 5.1 : 1)	13%
Me_3Al (5.0) + CuI·2LiCl (2.5)	23 h	97% (*Z*/*E* = >19 : 1)	0%
MeMgBr (2.5) + CuI (0.2)	1 h	86% (*Z*/*E* = 18 : 1)	0%

Scheme 6.



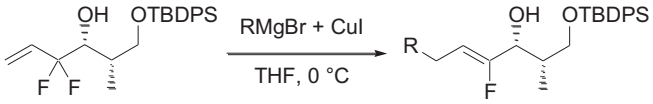
Scheme 7.

difluorohomoallyl alcohol **11** has some limitations concerning the availability of the reagents, long reaction time, as well as side reaction in the case of alkyllithium. To solve these problems, we examined Grignard reagents, while we had found that Grignard reagent provided a complicated mixture with the inner olefinic substrate **1** (Scheme 1) [13]. To our delight, in the case of the vinyl type substrate **11** defluorinative allylic alkylation smoothly proceeded by the reaction with Grignard reagent in the presence of a catalytic amount of CuI in THF [27]. Results obtained with the substrate ***syn*-11a** are summarized in Table 2. Survey of reaction conditions is briefly mentioned in the cases of PhMgBr (entries 1–3). Reaction of the hydroxy free substrate ***syn*-11a** with one equimolar amount of PhMgBr resulted in recovery of the starting material, indicating the quantitative and rapid formation of magnesium alkoxide (entry 2). As a result, more than two molar equivalent of Grignard reagent is required. The vinyl type substrate **11** showed fairly high reactivity toward Grignard reagent as compared with trialkylaluminium, which did not react in THF at 0 °C in the absence of CuI. That is, even in the absence of CuI, PhMgBr reacted in THF at 0 °C for 1.5 h to give the phenylated product ***syn*-12b** in 36% yield (*Z*/*E* = 7:1), although both product yield and stereoselectivity were not a satisfactory level (entry 3). Addition of Cu(I) promoted the reaction very effectively [28]. As a copper salt, CuI was reactive enough in the present cases and the optimized condition was the combined use of 2.5 molar equivalent of Grignard reagent and a catalytic amount (20 mol%) of CuI. Under these conditions the phenylated product ***syn*-12b** was obtained in 87% yield with high *Z* selectivity (*Z*/*E* = 10:1, entry 1) after the reaction in THF at 0 °C for 1 h. Much higher *Z* selectivity (*Z*/*E* = >17:1) was observed in the reactions of alkyl Grignard reagent such as methyl, isobutyl and isopropyl derivative (entries 4–6). As in the case of the phenyl derivative ***syn*-12b**, separation of the *Z*/*E* mixture of the product **12** was carried out by MPLC on silica gel. Furthermore, in all cases using ***syn*-11a** (99% ee) as the starting material, epimerization of the chiral center as well as the decrease in optical purity of the products **12a-d** were not observed as determined by chiral HPLC analysis.

Under the optimized conditions for the Grignard reagent (Table 2, entry 1), similar reactions were conducted using the other isomer ***anti*-11a** and the results are shown in Table 3. Allylic substitution took place smoothly to give the desired products ***anti*-12a-d** in good yields with high *Z* selectivity without any observable epimerization and the decrease in optical purity. Separation of the *Z*/*E* mixture of the product was also carried out by MPLC (silica gel).

As described above, in the presence of a catalytic amount of CuI (20 mol%) Grignard reagent smoothly reacted with vinyl type difluorohomoallyl alcohol **11** under mild conditions (0 °C, 1 h) to

Table 2
Defluorinative allylic alkylation of ***syn*-11a** with RMgBr + CuI system.

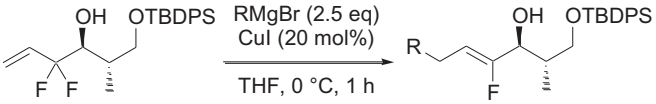


***syn*-11a** ***syn*-12**

Entry	RMgBr (equiv)	CuI (equiv)	Time (h)	***syn*-12**	Yield[a] (%)	*Z*/*E*[b]
1	PhMgBr (2.5)	0.2	1	***syn*-12b**	87	10:1
2	PhMgBr (1.0)	0.2	1	***syn*-12b**	0[c]	
3	PhMgBr (2.5)	None	1.5	***syn*-12b**	36	7:1
4	MeMgBr (2.5)	0.2	1	***syn*-12a**	86	18:1
5	*i*-BuMgBr (2.5)	0.2	1	***syn*-12c**	76	17:1
6	*i*-PrMgBr (2.5)	0.2	1	***syn*-12d**	93	18:1

[a] Isolated yield.
[b] Ratio was determined by 300 MHz ^{1}H NMR of the crude mixture.
[c] Recovery of the starting material ***syn*-11a**.

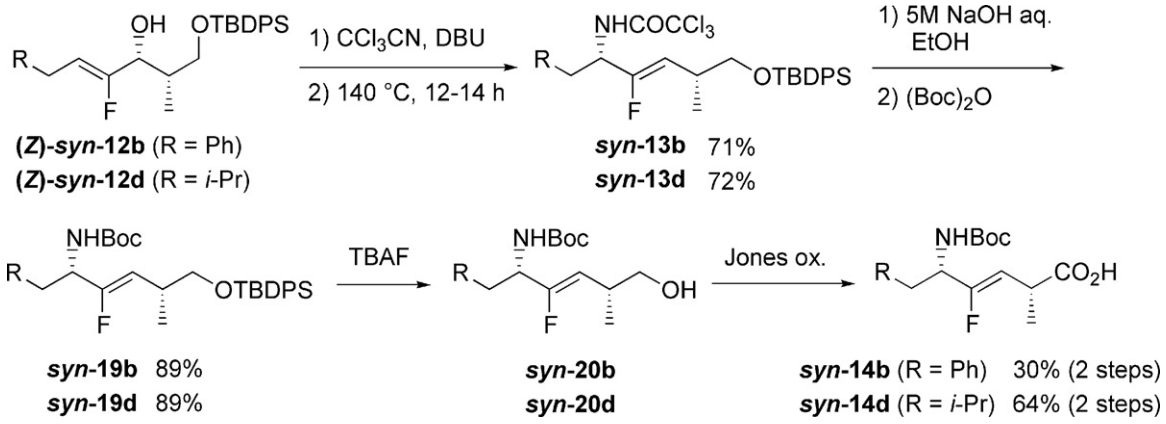
Table 3
Defluorinative allylic alkylation of ***anti*-11a** with RMgBr + CuI system.



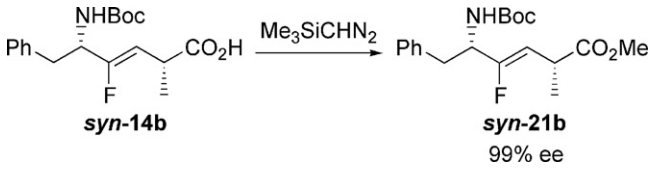
***anti*-11a** ***anti*-12**

Entry	RMgBr	***anti*-12**	Yield[a] (%)	*Z*/*E*[b]
1	PhMgBr	***anti*-12b**	87	11:1
2	MeMgBr	***anti*-12a**	76	19:1
3	*i*-BuMgBr	***anti*-12c**	76	11:1
4	*i*-PrMgBr	***anti*-12d**	99	14:1

[a] Isolated yield.
[b] Ratio was determined by 300 MHz ^{1}H NMR of the crude mixture.



Scheme 8.



Scheme 9.

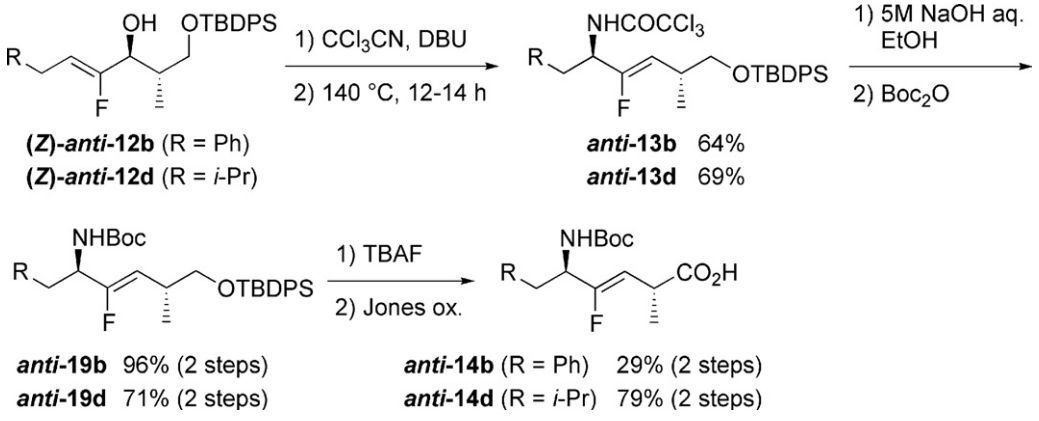
give the allylic substitution product **12** in high yield and high *Z* selectivity without any regio isomer and observable side reactions. In addition to these efficacies, availability of a variety of alkyl, alkenyl and aryl Grignard reagents would also make the present reaction as one of the promising methods for such functionalized fluorinated olefinic compounds.

2.2. Preparation of AA–ψ[(Z)–CF = CH]–Ala via imidate Claisen rearrangement

Next we examined the conversion of the allylic alcohol **12** into the fluoroalkene dipeptide form through imidate Claisen rearrangement (Overman rearrangement) [6,7,29].

Employing the standard procedure for the imidate Claisen rearrangement conversion of the hydroxy group into the amino group was performed (Scheme 8). Thus, the reaction of **(*Z*)-*syn*-12b** with trichloroacetonitrile and DBU gave the trichloroimidate, which was stable enough to be purified by column chromatography on silica gel before subjected to the rearrangement reaction. Thermal reaction of the purified imidate in xylenes at 140 °C for 14 h provided the rearranged trichloroacetoamide ***syn*-13b** as a single isomer in 71% yield. Alkaline hydrolysis of trichloroacetoamide using 5 M NaOH in EtOH at room temperature for 2 h followed by the reaction of the crude product with Boc_2O and triethylamine gave the *N*-Boc derivative ***syn*-19b** in good yield (89%). Desilylation of the silyl ether ***syn*-19b** by treatment with TBAF in THF gave the free alcohol ***syn*-20b** in quantitative yield. Oxidation of the primary alcohol into the carboxylic acid by Jones reagent gave the desired final compound ***syn*-14b**, but in low yield (30% yield) presumably mainly due to the oxidation of benzylic position at the same time. The dipeptide isostere ***syn*-14b** is corresponding to the dipeptide Boc-L-Phe-L-Ala-OH. Likewise, **(*Z*)-*syn*-12d** was also converted in 72% yield into rearranged product ***syn*-13d** in a stereoselective manner without the decrease in optical purity. In the final step with this alkyl derivative ***syn*-13d**, Jones oxidation worked nicely to give the desired carboxylic acid ***syn*-14d** in 64% yield, which is corresponding to the dipeptide Boc-L-Leu-L-Ala-OH (Scheme 8).

Relative configuration and optical purity of ***syn*-14b** were determined as follows. By comparing NMR data of ***syn*-20b** synthesized here and ***anti*-20b** previously synthesized in a racemic form [13], the relative configuration between 2 position (Me-substituted carbon) and 5 position (BocNH-substituted carbon) was confirmed. Next, conversion of ***syn*-14b** into the methyl ester ***syn*-21b** by treating with Me_3SiCHN_2 (quantitative yield) and the following HPLC analysis using a chiral column (CHIRALPAK AD-H) revealed the optical purity of ***syn*-21b** to be 99% ee (Scheme 9). In this synthesis we used commercially available methyl (*S*)-3-hydroxy-2-methylpropionate **15** as the starting material, whose optical purity was 99% ee. Thus, not only a complete chiral transfer in the imidate Claisen rearrangement, but also no racemization in each step was confirmed.



Scheme 10.

Using the *anti* isomer **12** as the starting material, dipeptide isosteres containing unnatural D series of amino acids can be synthesized. Thus, employing essentially the same procedures, ***anti*-12b** and ***anti*-12d** were successfully converted into the fluoroalkene dipepptide isostere forms ***anti*-14b** and ***anti*-14d** corresponding to Boc-D-AA-L-Ala-OH (AA = Phe and Leu, respectively) (Scheme 10).

3. Conclusion

We have demonstrated an efficient method for the preparation of (*Z*)-fluoroalkene dipeptide isosteres in optically pure form. Followings are key features of the present method. Defluorinative allylic alkylation of each diastereomer of the difluorohomoallyl alcohol **11** obtained by difluoroallylation of the optically pure *O*-silylated (*S*)-2-methyl-3-hydroxypropanal **10a** with the bromodifluoropropene-indium system efficiently proceeded by the reaction of Grignard reagent and a catalytic amount of CuI system in THF to give the allylic alcohol **12** in high yield and in excellent *Z* selective manner without any regio isomer. Subsequent imidate Claisen rearrangement of the allylic alcohol proceeded with a complete 1,3-chirality transfer to give the fluoroalkene dipeptide isostere structure **14** after the final conversion of the primary alcohol into carboxylic acid form.

4. Experimental

4.1. General

All reactions were carried out under argon atmosphere. ^{1}H and ^{13}C NMR spectra were taken on a Bruker dpx400 spectrometer or Varian Mercury300 spectrometer, and chemical shifts were reported in parts per million (ppm) using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^{1}H NMR, and $CDCl_3$ (77.01 ppm) for ^{13}C-NMR as an internal standard, respectively. ^{19}F NMR spectra were taken on a Bruker dpx400 spectrometer, and chemical shifts were reported in parts per million using trifluoromethylbenzene (0 ppm) as a standard. Infrared (IR) spectra were recorded on a JASCO FT/IR-620 infrared spectrophotometer. Mass spectra (MS) were obtained on a Micromass LCT system (ESI-TOF). Medium pressure liquid chromatography (MPLC) was performed using prepacked column (silica gel, 50 μm) with RI detector.

4.2. (*R*)-3-{[tert-Butyl(diphenyl)silyl]oxy}-2-methyl-1-propanol 16 [20]

Under argon atmosphere to a solution of (*S*)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-2-methylpropanoate (11.0 g, 30 mmol) in toluene (150 ml) was added diisobutylaluminium hydride (0.9 M solution in hexane, 64 ml, 60 mmol) dropwise at −78 °C and then the whole was stirred for 5 h at the same temperature. The reaction mixture was quenched by addition of 1 M HCl (30 ml) and extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$, concentrated under reduced pressure to leave the residue, which was purified by silica gel column chromatography (hexane/EtOAc = 7:1) to give **16** in 89% yield (8.8 g, 27 mmol). ^{1}H NMR data was identical to those reported in the literature [20]. Optical purity analyzed by HPLC using chiral column (CHIRALPAK AD-H, 25 cm × 0.46 cm i.d.; eluted by 1% *i*-PrOH in hexane) was determined to be 99% ee by comparing with the racemic compound.

4.3. (2*S*,3*S*)-1-{[tert-Butyl(diphenyl)silyl]oxy}-4,4-difluoro-2-methylhex-5-en-3-ol *anti*-11a and (2*S*,3*R*)-1-{[tert-butyl(diphenyl)silyl]oxy}-4,4-difluoro-2-methylhex-5-en-3-ol *syn*-11a

Under argon atmosphere to a solution of Dess-Martin periodinane (7.9 g, 19 mmol) in CH_2Cl_2 (27 ml) was added to a solution of the alcohol **16** (4.0 g, 12 mmol) in CH_2Cl_2 (10 ml) at room temperature. Then, after being stirred for 30 min at room temperature, the reaction mixture was diluted by the addition of Et_2O. Precipitates were filtered off and the filtrate was concentrated under reduced pressure to leave crude aldehyde **10a**, which was used immediately without further purification.

Under argon atmosphere to indium mesh (4.2 g, 37 mmol) in DMF (115 ml) was added 3-bromo-3,3-difluoropropene (3.8 ml, 37 mmol) at room temperature and the whole was stirred for additional 10 min. Then, to this mixture was added the crude aldehyde **10a** and the whole was stirred for 3 h at room temperature. Insoluble precipitates were filtered off with the aid of celite after the addition of water and Et_2O. The filtrate was extracted with Et_2O and the organic extracts were washed with brine, dried over $MgSO_4$, concentrated under reduced pressure to leave the residue, which was purified by silica gel column chromatography (hexane/EtOAc = 30:1) to give a *syn*/*anti* mixture of **11a** in 84% yield (4.2 g, 11 mmol, *syn*/*anti* = 1.6:1). Further purification by MPLC (hexane/EtOAc = 20:1) gave pure ***anti*-11a** and ***syn*-11a**, respectively. In a separate experiment racemic **11a** was prepared by using the racemic aldehyde **10a**. Optical purity of each isomer was determined by HPLC analysis using chiral column (CHIRALPAK AD-H, 25 cm × 0.46 cm i.d.; 1% *i*-PrOH in hexane; flow rate, 0.3 ml/min). Retention time; (2*S*,3*S*)-***anti*-11a**; t_R = 18.4 min and (2*R*,3*R*)-***anti*-11a**; t_R = 22.9 min, respectively, and (2*S*,3*R*)-***syn*-11a**; t_R = 21.6 min and (2*R*,3*S*)-***syn*-11a**; t_R = 23.8 min, respectively.

(2*S*,3*S*)-***anti*-11a.** Colorless oil; $[\alpha]_D^{25}$ = −36.5 (*c* = 1.0, $CHCl_3$); IR (neat) ν 3453 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (9H, s), 1.09 (3H, d, *J* = 6.4 Hz), 2.03 (1H, dqdd, *J* = 7.1, 6.4, 6.4, 3.7 Hz), 3.67 (1H, dd, *J* = 10.6, 6.4 Hz), 3.80 (1H, dddd, *J* = 7.1, 7.1, 7.1, 7.0 Hz), 4.00 (1H, dd, *J* = 10.3, 3.7 Hz), 4.25 (1H, d, *J* = 7.0 Hz), 5.51 (1H, d, *J* = 11.6 Hz), 5.73 (1H, d, *J* = 17.4 Hz), 6.09 (1H, dddd, *J* = 17.4, 11.8, 11.8, 11.6 Hz), 7.39–7.46 (6H, m), 7.67–7.70 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 19.1, 26.8, 34.6, 68.0, 77.6 (*t*, *J* = 31.8 Hz), 120.2 (*t*, *J* = 9.5 Hz), 120.4 (*t*, *J* = 244.2 Hz), 127.8, 130.0, 130.9 (*t*, *J* = 25.8 Hz), 132.5, 135.6, 135.7; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −48.9 (1F, ddd, *J* = 250.1, 11.8, 7.1 Hz),−42.1 (1F, ddd, *J* = 250.1, 11.8, 7.1 Hz); MS (ESI-TOF) *m*/*z* 405 $[M+H]^+$; HRMS calcd for $C_{23}H_{31}F_2O_2Si$ $[M+H]^+$: 405.2061, found: 405.2085. Anal. Calcd for $C_{23}H_{30}F_2O_2Si$: C, 68.28; H, 7.47. Found: C, 68.43; H, 7.50.

(2*S*,3*R*)-***syn*-11a.** Colorless oil; $[\alpha]_D^{25}$ = −30.0 (*c* = 1.0, $CHCl_3$); IR (neat) ν 3476 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, d, *J* = 7.0 Hz), 1.07 (9H, s), 2.10 (1H, dqdd, *J* = 7.0, 7.0, 6.4, 2.1 Hz), 2.52 (1H, d, *J* = 5.1 Hz), 3.65 (1H, dd, *J* = 10.0, 6.4 Hz), 3.69 (1H, dd, *J* = 10.3, 7.0 Hz), 4.14 (1H, dddd, *J* = 12.7, 12.7, 5.1, 2.1 Hz), 5.51 (1H, d, *J* = 11.5 Hz), 5.73 (1H, d, *J* = 17.4 Hz), 6.09 (1H, dddd, *J* = 17.4, 11.5, 11.4, 11.4 Hz), 7.38–7.45 (6H, m), 7.65–7.69 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1, 19.2, 26.9, 35.3, 67.6, 73.5 (*t*, *J* = 27.8 Hz), 120.4 (*t*, *J* = 9.5 Hz), 120.5 (*t*, *J* = 243.7 Hz), 127.8, 129.8, 131.1 (*t*, *J* = 25.9 Hz), 133.1, 133.2, 135.5, 135.6; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −48.6 (1F, ddd, *J* = 249.8, 12.7, 11.4 Hz), −47.1 (1F, ddd, *J* = 249.8, 12.7, 11.4 Hz); MS (ESI-TOF) *m*/*z* 405.2 $[M+H]^+$; HRMS calcd for $C_{23}H_{31}F_2O_2Si$ $[M+H]^+$: 405.2061, Found: 405.2071. Anal. Calcd for $C_{23}H_{30}F_2O_2Si$: C, 68.28; H, 7.47. Found: C, 68.22; H, 7.56.

4.4. Copper-mediated allylic alkylation of 11 with organometallics

4.4.1. (2*S*,3*R*,*Z*)-1-{[tert-Butyl(diphenyl)silyl]oxy}-4-fluoro-2-methyl-6-phenylhex-4-en-3-ol (*Z*)-*syn*-12b and (2*S*,3*R*,*E*)-1-{[tert-butyl(diphenyl)silyl]oxy}-4-fluoro-2-methyl-6-phenylhex-4-en-3-ol (*E*)-*syn*-12b

Under argon atmosphere a mixture of ***syn*-11a** (99% ee, 202 mg, 0.50 mmol), CuI (19 mg, 0.10 mmol) and PhMgBr (1.0 M solution in THF, 1.3 ml, 1.3 mmol) in THF (2.5 ml) was stirred at 0 °C for 1 h. To the reaction mixture was added saturated NH_4Cl solution (10 ml). After the extraction with Et_2O (10 ml × 3), the organic extracts were washed with brine, dried over $MgSO_4$, concentrated under

reduced pressure to leave a residue, which was purified by silica gel column chromatography (hexane/EtOAc = 40: 1) and then by MPLC (hexane/EtOAc = 20:1) to give **(*Z*)-*syn*-12b** (183 mg, 0.40 mmol, 79% yield) and **(*E*)-*syn*-12b** (18 mg, 0.04 mmol, 8% yield) in the order of elution.

(*Z*)-*syn*-12b. Colorless oil; $[\alpha]_D^{25}$ +4.5 (c = 1.0, $CHCl_3$); IR (neat) ν 3476, 3070, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, d, J = 7.1 Hz), 1.11 (9H, s), 2.12–2.22 (1H, m), 3.27 (1H, brs), 3.45–3.60 (2H, m), 3.80 (2H, d, J = 5.4 Hz), 4.49 (1H, d, J = 10.0 Hz), 5.18 (1H, dt, J = 37.0, 10.0 Hz), 7.24–7.27 (3H, m), 7.29–7.33 (2H, m), 7.42–7.49 (6H, m), 7.70–7.72 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8, 19.1, 26.8, 29.5 (d, J = 5.7 Hz), 37.5, 67.8, 72.7 (d, J = 32.9 Hz), 105.2 (d, J = 12.5 Hz), 126.0, 127.8, 128.3, 128.4, 129.9, 132.9 (d, J = 14.2 Hz), 135.6 (d, J = 9.7 Hz), 140.3, 158.8 (d, J = 256.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −59.6 (1F, dd, J = 37.0, 10.0 Hz); MS (ESI-TOF) m/z 463 $[M+H]^+$; HRMS calcd for $C_{29}H_{36}FO_2Si$ $[M+H]^+$: 463.2482, found: 463.2469.

(*E*)-*syn*-12b. Colorless oil; IR (neat) ν 3465, 3070, 2931, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, d, J = 6.9 Hz), 1.07 (9H, s), 2.15–2.21 (1H, m), 3.34 (1H, dd, J = 15.9, 7.5 Hz), 3.45 (1H, dd, J = 15.9, 8.7 Hz), 3.66 (1H, dd, J = 10.2, 4.6 Hz), 3.77 (1H, dd, J = 10.0, 7.8 Hz), 4.75 (1H, dd, J = 25.0, 4.8 Hz), 5.41 (1H, m), 7.18–7.21 (3H, m), 7.26–7.29 (2H, m), 7.38–7.45 (6H, m), 7.66–7.70 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 19.1, 26.8, 30.8 (d, J = 9.5 Hz), 39.2, 67.2, 69.6 (d, J = 27.3 Hz), 107.4 (d, J = 22.1 Hz), 126.3, 127.8, 128.1, 128.5, 129.8, 129.8, 132.9, 133.1, 135.5, 135.7, 139.8, 159.0 (d, J = 252.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −54.9 (1F, t, J = 25.0 Hz); MS (ESI-TOF) m/z 463 $[M+H]^+$; HRMS calcd for $C_{29}H_{36}FO_2Si$ $[M+H]^+$: 463.2324, found: 463.2469.

4.4.2. (2S,3S,Z)-1-{[tert-Butyl(diphenyl)silyl]oxy}-4-fluoro-2-methyl-6-phenylhex-4-en-3-ol (Z)-anti-12b and (2S,3S,E)-1-{[tert-butyl(diphenyl)silyl]oxy}-4-fluoro-2-methyl-6-phenylhex-4-en-3-ol (E)-anti-12b

By the similar procedure for the preparation of ***syn*-12b**, reaction of ***anti*-11a** (99% ee, 202 mg, 0.50 mmol), PhMgBr (1.0 M solution in THF, 1.3 ml, 1.3 mmol) and CuI (19 mg, 0.10 mmol) provided **(*Z*)-*anti*-12b** (179 mg, 0.39 mmol, 77% yield) and **(*E*)-*anti*-12b** (16 mg, 0.034 mmol, 6.8% yield), respectively after the chromatographic purification by silica gel column (hexane/EtOAc = 40:1) followed by MPLC (hexane/EtOAc = 20:1).

(*Z*)-*anti*-12b. Colorless oil; $[\alpha]_D^{25}$ +5.3 (c = 1.0, $CHCl_3$); IR (neat) ν 3465, 3070, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.18 (3H, d, J = 7.0 Hz), 0.93 (9H, s), 1.95–2.02 (1H, m), 3.51 (1H, dd, J = 10.3, 6.7 Hz), 3.68 (1H, dd, J = 10.3, 3.6 Hz), 4.00 (1H, dd, J = 18.0, 7.3 Hz), 5.02 (1H, dt, J = 37.0, 7.6 Hz), 7.05–7.17 (5H, m), 7.24–7.32 (6H, m), 7.53–7.55 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.1, 26.8, 29.7 (d, J = 5.4 Hz), 37.2, 68.1, 76.0 (d, J = 29.7 Hz), 106.7 (d, J = 13.1 Hz), 126.1, 127.8, 128.3, 128.5, 129.9, 132.6 (d, J = 3.8 Hz), 135.6 (d, J = 3.7 Hz), 140.1, 159.7 (d, J = 259.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.1 (1F, dd, J = 37.0, 18.0 Hz); MS (ESI-TOF) m/z 485 $[M+Na]^+$; HRMS calcd for $C_{29}H_{35}FNaO_2Si$ $[M+Na]^+$: 485.2278, found: 485.2288. Anal. Calcd for $C_{29}H_{35}FO_2Si$: C, 75.28; H, 7.62. Found: C, 75.29; H, 7.59.

(*E*)-*anti*-12b. Colorless oil; IR (neat) ν cm^{-1}: 3465, 3068, 1704, 823; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, d, J = 7.0 Hz), 1.07 (9H, s), 2.13–2.19 (1H, m), 3.38 (1H, dd, J = 15.8, 8.2 Hz), 3.43–3.49 (1H, m), 3.69 (1H, dd, J = 10.2, 7.4 Hz), 3.72 (1H, brs), 3.88 (1H, dd, J = 10.2, 3.9 Hz), 4.51–4.60 (1H, m), 5.43 (1H, dt, J = 22.0, 8.2 Hz), 7.19–7.30 (5H, m), 7.39–7.45 (6H, m), 7.68–7.70 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 19.1, 26.8, 31.0 (d, J = 9.3 Hz), 37.7, 68.3, 71.4 (d, J = 27.3 Hz), 108.1 (d, J = 22.1 Hz), 126.1, 127.8, 128.2, 128.6, 129.9, 132.7, 132.8, 135.6, 139.8, 158.8 (d, J = 158.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −59.6 (1F, dd, J = 28.0, 22.0 Hz); MS (ESI-TOF) m/z 463 $[M+H]^+$; HRMS calcd for $C_{29}H_{36}FO_2Si$ $[M+H]^+$: 463.2438, found: 463.2469.

4.4.3. (2S,3R,Z)-1-{[tert-Butyl(diphenyl)silyl]oxy}-4-fluoro-2,7-dimethyloct-4-en-3-ol (Z)-syn-12d and (2S,3R,E)-1-{[tert-butyl(diphenyl)silyl]oxy}-4-fluoro-2,7-dimethyloct-4-en-3-ol (E)-syn-12d

By the similar procedure for the preparation of ***syn*-12b**, reaction of ***syn*-11a** (99% ee, 202 mg, 0.50 mmol), *i*-PrMgBr (1.0 M solution in THF, 1.3 ml, 1.3 mmol) and CuI (19 mg, 0.10 mmol) provided **(*Z*)-*syn*-12c** (195 mg, 0.44 mmol, 88% yield) and **(*E*)-*syn*-12c** (11 mg, 0.025 mmol, 5% yield), respectively after the chromatographic purification by silica gel column (hexane/EtOAc = 40:1) followed by MPLC (hexane/EtOAc = 20:1).

(*Z*)-*syn*-12d. Colorless oil; $[\alpha]_D^{25}$ +1.3 (c = 1.0, $CHCl_3$); IR (neat) ν 3467, 3072, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (6H, d J = 6.7 Hz), 0.98 (3H, d, J = 7.1 Hz), 1.12 (9H, s), 1.60–1.75 (1H, m), 2.02–2.10 (2H, m), 2.12–2.17 (1H, m), 3.28 (1H, brs), 3.79 (2H, d, J = 5.3 Hz), 4.44 (1H, dd, J = 11.0, 3.2 Hz), 4.95 (1H, dt, J = 38.5, 7.7 Hz), 7.41–7.50 (6H, m), 7.71–7.74 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 19.1, 22.2 (d, J = 3.6 Hz), 26.8, 28.4, 32.2 (d, J = 4.0 Hz), 37.6, 67.7, 72.8 (d, J = 33.4 Hz), 104.9 (d, J = 12.9 Hz), 127.8, 127.8, 129.8, 132.8, 133.0, 135.5, 135.6, 158.7 (d, J = 254.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −59.8 (1F, dd, J = 38.5, 11.0 Hz); MS (ESI-TOF) m/z 429 $[M+H]^+$; HRMS calcd for $C_{26}H_{38}FO_2Si$ $[M+H]^+$: 429.2597, found: 429.2625.

(*E*)-*syn*-12d. Colorless oil; IR (neat) ν 3452, 3071, 827 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89–0.94 (9H, m), 1.08 (9H, s), 1.59–1.64 (1H, m), 1.86–1.93 (2H, m), 2.13–2.16 (1H, m), 2.96 (1H, brs), 3.61 (1H, dd, J = 10.1, 4.7 Hz), 3.75 (1H, dd, J = 10.1, 8.0 Hz), 4.64 (1H, dd, J = 25.0, 4.9 Hz), 5.20 (1H, dt, J = 23.2, 8.1 Hz), 7.38–7.46 (6H, m), 7.67–7.71 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1, 19.2, 22.0, 22.3, 26.8, 28.8, 33.9 (d, J = 8.0 Hz), 39.4, 67.0, 69.0 (d, J = 26.5 Hz), 107.3 (d, J = 19.8 Hz), 127.7, 129.7, 129.8, 133.0, 133.3, 135.5, 135.7, 158.6 (d, J = 251.1 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −56.4 (1F, m); MS (ESI-TOF) m/z 429 $[M+H]^+$; HRMS calcd for $C_{26}H_{38}FO_2Si$ $[M+H]^+$: 429.2640, found: 429.2625. Anal. Calcd for $C_{26}H_{37}FO_2Si$: C, 72.85; H, 8.70. Found: C, 72.67; H, 8.36.

4.4.4. (2S,3S,Z)-1-{[tert-Butyl(diphenyl)silyl]oxy}-4-fluoro-2,7-dimethyloct-4-en-3-ol (Z)-anti-12d and (2S,3S,E)-1-{[tert-butyl(diphenyl)silyl]oxy}-4-fluoro-2,7-dimethyloct-4-en-3-ol (E)-anti-12d

By the similar procedure for the preparation of ***syn*-12d**, reaction of ***anti*-11a** (99% ee, 202 mg, 0.50 mmol), *i*-PrMgBr (1.0 M solution in THF, 1.3 ml, 1.3 mmol) and CuI (19 mg, 0.10 mmol) provided **(*Z*)-*anti*-12d** (205 mg, 0.46 mmol, 92% yield) and **(*E*)-*anti*-12d** (15 mg, 0.03 mmol, 6.7% yield), respectively after the chromatographic purification by silica gel column (hexane/EtOAc = 40: 1) followed by MPLC (hexane/EtOAc = 20:1).

(*Z*)-*anti*-12d. Colorless oil; $[\alpha]_D^{25}$ +18.6 (c = 1.0, $CHCl_3$); IR (neat) ν 3475, 3070, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92–0.95 (9H, m), 1.09 (9H, s), 1.63–1.70 (1H, m), 2.02–2.13 (3H, m), 3.65 (1H, dd, J = 10.2, 6.7 Hz), 3.90 (1H, dd, J = 10.2, 3.7 Hz), 3.95 (1H, brs), 4.10 (1H, dd, J = 18.0, 6.7 Hz), 4.94 (1H, dt, J = 37.0, 7.7 Hz), 7.40–7.48 (6H, m), 7.70 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 19.1, 22.2, 22.3, 26.8, 28.3, 32.3 (d, J = 3.5 Hz), 37.2, 68,1, 76.1 (d, J = 30.6 Hz), 106.6 (d, J = 13.8 Hz), 127.8, 129.8, 132.6, 135.6, 159.0 (d, J = 257.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.5 (1F, dt, J = 37.0, 18.0 Hz); MS (ESI-TOF) m/z 429 $[M+H]^+$; HRMS calcd for $C_{26}H_{38}FO_2Si$ $[M+H]^+$: 429.2645, found: 429.2625. Anal. Calcd for $C_{26}H_{37}FO_2Si$: C, 72.85; H, 8.70. Found: C, 72.47; H, 8.65.

(*E*)-*anti*-12d. Colorless oil; IR (neat) ν 3466, 3071, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, d, J = 6.9 Hz), 0.91 (3H, d, J = 6.0 Hz), 0.93 (3H, d, J = 5.6 Hz), 1.08 (9H, s), 1.60–1.67 (1H, m), 1.91–1.96 (2H, m), 2.08–2.14 (1H, m), 3.69 (1H, dd, J = 10.2, 7.1 Hz), 3.88 (1H, dd, J = 10.2, 3.5 Hz), 4.45 (1H, dd, J = 28.2, 9.0 Hz), 5.24 (1H, dt, J = 22.5, 8.1 Hz), 7.36–7.48 (6H, m), 7.65–7.70 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 19.1, 22.1, 22.3, 26.8, 28.8, 34.0 (d,

J = 8.1 Hz), 37.7, 68.1, 71.0 (d, J = 27.2 Hz), 108.1 (d, J = 19.9 Hz), 127.8, 127.8, 129.9, 132.8, 132.9, 135.6, 158.4 (d, J = 251.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.6 (1F, m); MS (ESI-TOF) m/z 429 $[M+H]^+$; HRMS calcd for $C_{26}H_{38}FO_2Si$ $[M+H]^+$: 429.2629, found: 429.2625. Anal. Calcd for $C_{26}H_{37}FO_2Si$: C, 72.85; H, 8.70. Found: C, 72.56; H, 8.47

4.4.5. (2S*,3R*,Z)-1-{[tert-Butyl(diphenyl)silyl]oxy}-4-fluoro-2-methylhept-4-en-3-ol (Z)-syn-12a, (2S*,3R*,E)-1-{[tert-butyl(diphenyl)silyl]oxy}-4-fluoro-2-methylhept-4-en-3-ol (E)-syn-12a, and 1-{[tert-butyl(diphenyl)silyl]oxy}-2-methyl-5-hexen-3-one 18a

Under argon atmosphere to CuI (476 mg, 2.5 mmol) in THF (2 ml) was added MeLi (1.2 M solution in Et_2O, 4.2 ml, 5.0 mmol) at 0 °C. After being stirred for 15 min, the reaction mixture was treated with ***syn*-11a** (racemic, 202 mg, 0.5 mmol) for 4 h at the same temperature. Usual extractive workup (Et_2O for extraction) followed by purification by silica gel column (hexane/EtOAc = 20:1) gave **(*Z*)-*syn*-12a** (136 mg, 0.34 mmol, 67% yield), **(*E*)-*syn*-12a** (27.6 mg, 0.07 mmol, 14% yield) and **18a** (24.5 mg, 0.07 mmol, 13% yield), respectively.

(*Z*)-*syn*-12a. Colorless oil; IR (neat) ν 3450 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, d, J = 7.1 Hz), 1.00 (3H, *t*, J = 7.5 Hz), 1.08 (9H, s), 2.05–2.18 (3H, m), 3.15 (1H, d, J = 5.0 Hz), 3.74 (2H, d, J = 5.2 Hz), 4.37 (1H, ddd, J = 11.2, 5.0, 4.2 Hz), 4.90 (1H, dt, J = 38.7, 7.5 Hz), 7.39–7.45 (6H, m), 7.66–7.70 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 14.2, 16.7 (d, J = 5.6 Hz), 19.2, 26.8, 37.6, 67.8, 72.8 (d, J = 33.0 Hz), 108.1 (d, J = 12.9 Hz), 127.8, 129.8, 132.9, 133.0, 135.5, 135.6, 157.8 (d, J = 253.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.9 (1F, dd, J = 38.7, 11.2 Hz); MS (ESI-TOF) m/z 401 $[M+H]^+$; HRMS calcd for $C_{24}H_{34}FO_2Si$ $[M+H]^+$: 401.2312, found: 401.2329. Anal. Calcd for $C_{24}H_{33}FO_2Si$: C, 71.96; H, 8.30. Found: C, 71.93; H, 8.42.

(*E*)-*syn*-12a. Colorless oil; IR (neat) ν 3419 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, J = 7.0 Hz), 0.98 (3H, dd, J = 7.6, 7.6 Hz), 1.07 (9H, s), 1.99 (1H, dqd, J = 15.2, 7.6, 7.6 Hz), 2.05 (1H, dqd, J = 15.2, 7.6, 7.6 Hz), 2.12–2.19 (1H, m), 3.11 (1H, d, J = 3.8 Hz), 3.58 (1H, dd, J = 10.9, 6.2 Hz), 3.65 (1H, dd, J = 10.9, 8.9 Hz), 4.56–4.68 (1H, m), 5.18 (1H, ddd, J = 24.5, 8.0, 8.0 Hz), 7.38–7.45 (6H, m), 7.66–7.74 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 14.7, 18.4 (d, J = 9.0 Hz), 19.1, 26.8, 39.3, 67.2, 69.4 (d, J = 26.7 Hz), 110.3 (d, J = 19.8 Hz), 127.7, 129.7, 129.8, 133.0, 133.2, 135.5, 135.7, 157.8 (d, J = 250.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.8 (1F, *t*, J = 24.5 Hz); MS (ESI-TOF) m/z 401 $[M+Na]^+$; HRMS calcd for $C_{24}H_{33}FO_2NaSi$ $[M+Na]^+$: 401.2312, found: 401.2299.

18a. Colorless oil; IR (neat) ν 1717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, d, J = 6.7 Hz), 1.04 (9H, s), 2.88 (1H, dqd, J = 7.8, 6.7, 5.5 Hz), 3.27 (1H, dd, J = 16.4, 6.2 Hz), 3.33 (1H, dd, J = 16.4, 6.2 Hz), 3.66 (1H, dd, J = 9.9, 5.5 Hz), 3.82 (1H, dd, J = 9.9, 7.8 Hz), 5.11 (1H, dd, J = 17.2, 1.4 Hz), 5.18 (1H, dd, J = 10.2, 1.4 Hz), 5.95 (1H, dddd, J = 17.2, 10.2, 6.2, 6.2 Hz), 7.37–7.46 (6H, m), 7.63–7.66 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 19.2, 26.8, 47.4, 48.1, 66.2, 118.6, 127.7, 129.7, 130.7, 133.2, 133.4, 135.6, 211.1; MS (ESI-TOF) m/z 389 $[M+Na]^+$; HRMS calcd for $C_{23}H_{30}O_2NaSi$ $[M+Na]^+$: 389.1913, found: 389.1912.

4.4.6. (Z)-1-{[tert-Butyl(diphenyl)silyl]oxy}-4-fluoro-8-methylnon-4-en-3-ol (Z)-17c

Under argon atmosphere to a mixture of **11b** (391 mg, 1.0 mmol), *i*-Bu_3Al (1.0 M solution in hexane, 5.0 ml, 5.0 mmol) was added a solution of CuI (248 mg, 2.5 mmol) and LiCl (212 mg, 5.0 mmol) in THF (2 ml) and the reaction mixture was stirred for 48 h at 0 °C. Extractive workup (Et_2O for extraction) followed by purification by silica gel column (hexane/EtOAc = 20:1) gave a *Z*/*E* mixture of **17c** in 84% yield (360 mg, 0.84 mmol, *Z*/*E* = 17:1). Colorless oil; IR (neat) ν 3421 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (6H, d, J = 6.6 Hz), 1.07 (9H, s), 1.27 (2H, dt, J = 7.6, 7.6 Hz), 1.53–1.65 (1H, m), 1.85–2.00 (2H, m), 2.12 (2H, dt, J = 7.6, 7.6 Hz), 3.24 (1H, d, J = 4.6 Hz), 3.82 (1H, dd, J = 10.6, 6.7, 4.1 Hz), 3.93 (1H, dd, J = 10.6, 6.5, 4.1 Hz), 4.37–4.45 (1H, m), 4.90 (1H, dt, J = 38.2, 7.6 Hz), 7.38–7.47 (6H, m), 7.67–7.69 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 21.2 (d, J = 4.7 Hz), 22.4, 26.8, 27.6, 35.7, 38.5, 62.3, 69.8 (d, J = 32.8 Hz), 106.2 (d, J = 13.4 Hz), 127.8, 129.9, 133.0, 133.1, 135.6, 159.1 (d, J = 254.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.5 (1F, dd, J = 38.2, 15.7 Hz); MS (ESI-TOF) m/z 429 $[M+H]^+$; HRMS calcd for $C_{26}H_{38}FO_2Si$ $[M+H]^+$: 429.2625, found: 429.2637. Anal. Calcd for $C_{26}H_{37}FO_2Si$: C, 72.85; H, 8.70, Found: C, 72.57; H, 8.52.

4.5. Imidate Claisen rearrangement

4.5.1. N-((2S,5R,Z)-6-{[tert-Butyl(diphenyl)silyl]oxy}-3-fluoro-5-methyl-1-phenylhex-3-en-2yl)-2,2,2-tri-chloroacetamide syn-13b

Under argon atmosphere a mixture of **(*Z*)-*syn*-12b** (231 mg, 0.50 mmol), DBU (0.11 ml, 0.75 mmol) and trichloroacetonitrile (0.09 ml, 0.90 mmol) in CH_2Cl_2 (2.5 ml) was stirred at room temperature for 1 h. The reaction mixture was extracted with Et_2O (10 ml × 3) after addition of a saturated NH_4Cl solution. The organic extracts were dried over $MgSO_4$, then evaporated under reduced pressure to leave the residue, which was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to give the imidate in 82% yield (247 mg, 0.41 mmol). Colorless oil; $[\alpha]_D^{25}$ +16.1 (c = 1.0, $CHCl_3$); IR (neat) ν 3342, 3068, 1666, 796 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04–1.17 (12H, m), 2.33–2.47 (1H, m), 3.45 (1H, dd, J = 15.7, 7.7 Hz), 3.56 (1H, dd, J = 15.7, 7.7 Hz), 3.67 (1H, dd, J = 10.0, 5.8 Hz), 3.69–3.77 (1H, m), 5.19 (1H, dt, J = 36.0, 7.7 Hz), 5.78 (1H, dd, J = 14.0, 5.3 Hz), 7.16–7.32 (5H, m), 7.37–7.50 (6H, m), 7.66–7.72 (4H, m), 8.51 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 19.7, 27.3, 30.0 (d, J = 5.3 Hz), 38.4, 65.4, 76.5 (d, J = 33.4 Hz), 91.9, 108.0 (d, J = 12.5 Hz), 126.6, 128.7, 128.9, 130.1, 133.9 (d, J = 7.2 Hz), 136.1 (d, J = 2.1 Hz), 140.2, 155.2 (d, J = 257.1 Hz), 161.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.2 (1F, dd, J = 36.0, 14.0 Hz); MS (ESI-TOF) m/z 606 $[M+H]^+$; HRMS calcd for $C_{31}H_{35}Cl_3FNO_2Si$ $[M+H]^+$: 606.1558, found: 606.1565.

After the imidate (507 mg, 0.83 mmol) in xylenes (10 ml) was refluxed (ca. 140 °C) for 14 h under argon atmosphere, evaporation under reduced pressure followed by purification by silica gel column chromatography (hexane/EtOAc = 50:1) gave ***syn*-13b** in 87% yield (444 mg, 0.73 mmol). Optical purity of ***syn*-13c** was determined to be 99% ee by HPLC analysis using chiral column (CHIRALPAK AD-H, 25 cm × 0.46 cm i.d.; 1% *i*-PrOH in hexane; flow rate, 1.0 ml/min). Colorless amorphous solid; $[\alpha]_D^{25}$ −5.0 (c = 1.0, $CHCl_3$); IR (neat) ν 3423, 3293, 3069, 1716, 823 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, d, J = 6.8 Hz), 1.07 (9H, s), 2.81–2.86 (1H, m), 2.97–3.01 (2H, m), 3.37 (1H, dd, J = 9.7, 6.7 Hz), 3.46 (1H, dd, J = 9.7, 5.6 Hz), 4.61 (1H, dd, J = 38.0, 9.5 Hz), 4.65–4.78 (1H, m), 6.76 (1H, brs), 7.18–7.24 (5H, m), 7.38–7.50 (6H, m), 7.67 (4H, *t*, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 19.3, 26.8, 31.9, 37.9, 53.5 (d, J = 29.7 Hz), 67.7, 92.3, 111.6 (d, J = 13.2 Hz), 127.1, 127.6, 128.5, 129.3, 129.6, 133.7, 135.4, 135.5, 154.4 (d, J = 255.6 Hz), 160.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.6 (1F, dd, J = 38.0, 18.0 Hz); MS (ESI-TOF) m/z 606 $[M+H]^+$; HRMS calcd for $C_{31}H_{36}Cl_3FNO_2Si$ $[M+H]^+$: 606.1591, found: 606.1565.

4.5.2. N-((2R,5R,Z)-6-{[tert-Butyl(diphenyl)silyl]oxy}-3-fluoro-5-methyl-1-phenylhex-3-en-2yl)-2,2,2-tri- chloroacetamide anti-13b

According to the procedure for the preparation of ***syn*-13b**, the imidate (4.5 g, 7.5 mmol, 75% yield) was prepared from **(*Z*)-*anti*-12b** (4.6 g, 10 mmol), DBU (2.6 ml, 17 mmol) and CCl_3CN (2.0 ml, 20 mmol). Colorless oil; $[\alpha]_D^{25}$ −16.1 (c = 1.0, $CHCl_3$); IR (neat) ν 3342, 3063, 1664, 827 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (9H, s), 1.16 (3H, d, 6.9), 2.34–2.47 (1H, m), 3.52 (2H, d, J = 7.6 Hz), 3.75 (1H, dd, J = 9.9, 3.5 Hz), 3.82 (1H, dd, J = 9.9, 5.0 Hz), 5.29 (1H, dt,

J = 35.0, 7.6 Hz), 5.54 (1H, dd, J = 22.0, 9.3 Hz), 7.18–7.27 (3H, m), 7.31 (2H, t, J = 7.3 Hz), 7.36 (6H, m), 7.67 (4H, t, J = 7.9 Hz), 8.50 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 19.3, 26.8, 29.7 (d, J = 4.7 Hz), 37.2, 64.3, 77.7 (d, J = 29.1 Hz), 91.5, 110.4 (d, J = 12.9 Hz), 126.2, 127.6, 128.3, 128.5, 129.6, 133.5, 135.7, 139.6, 154.5 (d, J = 258.8 Hz), 161.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.4 (1F, dd, J = 35.0, 22.0 Hz); MS (ESI-TOF) m/z: 606 $[M+H]^+$; HRMS calcd for $C_{31}H_{35}Cl_3FNO_2Si$ $[M+H]^+$: 606.1570, found: 606.1565. Anal. Calcd for $C_{31}H_{36}Cl_3FNO_2Si$: C, 61.33; H, 5.81; N, 2.31. Found: C, 61.31; H, 6.03; N, 2.22.

After a solution of the imidate (4.5 g, 7.5 mmol) in xylenes was refluxed for 14 h, the crude product was purified by silica gel column (hexane/EtOAc = 50:1) to give ***anti*-13b** in 85% yield (3.9 g, 6.4 mmol). Colorless oil. $[\alpha]_D^{25}$ +13.9 (c = 1.0, $CHCl_3$); IR (neat) ν 3426, 3070, 1710, 822 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, J = 6.8 Hz), 1.03 (9H, s), 2.78–2.85 (1H, m), 3.00–3.03 (2H, m), 3.44 (2H, d, J = 6.1 Hz), 4.51 (1H, dd, J = 38.0, 9.6 Hz), 4.62–4.72 (1H, m), 6.79 (1H, d, J = 8.5 Hz), 7.16–7.26 (5H, m), 7.36–7.62 (6H, m), 7.62–7.64 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 19.7, 27.3, 32.3, 38.5, 54.3 (d, J = 29.2 Hz), 68.2, 92.7, 112.5 (d, J = 13.2 Hz), 127.6, 128.1, 129.0, 129.8, 130.0, 134.1, 136.0, 136.0, 154.6 (d, J = 254.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.7 (1F, dd, J = 38.0, 19.0 Hz); MS (ESI-TOF) m/z 628 $[M+Na]^+$; HRMS calcd for $C_{29}H_{35}Cl_3FNNaO_2Si$ $[M+Na]^+$: 628.1416, found: 628.1384.

4.5.3. N-((1S,4R,Z)-5-{[tert-Butyl(diphenyl)silyl]oxy}-2-fluoro-1-isobutyl-4-methyl-2-pentenyl)-2,2,2-tri- chloroacetamide syn-13d

According to the procedure for the preparation of ***syn*-13b**, (***Z*)-*syn*-12d** (680 mg, 1.5 mmol), DBU (0.35 ml, 2.3 mmol) and CCl_3CN (0.28 ml, 2.8 mmol) provided the imidate in 84% yield (734 mg, 1.3 mmol). Colorless oil; $[\alpha]_D^{25}$ +21.0 (c = 1.0, $CHCl_3$); IR (neat) ν 3345, 3072, 1665, 826 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (6H, d, J = 6.7 Hz), 1.07–1.08 (12H, m), 1.61–1.64 (1H, m), 1.98–2.04 (2H, m), 2.32–2.35 (1H, m), 3.59 (1H, dd, J = 10.1, 5.7 Hz), 3.65 (1H, dd, J = 10.1, 6.8 Hz), 4.90 (1H, dt, J = 37.5, 7.8 Hz), 5.68 (1H, dd, J = 14.5, 5.5 Hz), 7.32–7.44 (6H, m), 7.65–7.69 (4H, m), 8.46 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 19.3, 22.1 (d, J = 16.2 Hz), 26.8, 28.3, 32.3 (d, J = 3.3 Hz), 37.9, 65.0, 76.4 (d, J = 34.0 Hz), 91.6, 107.7 (d, J = 12.9 Hz), 127.6, 129.6, 133.5, 133.6, 135.6, 135.6, 154.3 (d, J = 255.2 Hz), 161.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ–60.7 (1F, dd, J = 37.5, 14.5 Hz); MS (ESI-TOF) m/z 572 $[M + H]^+$; HRMS calcd for $C_{28}H_{38}Cl_3FNO_2Si$ $[M+H]^+$: 572.1740, found: 572.1721. Anal. Calcd for $C_{28}H_{37}Cl_3FNO_2Si$: C, 58.69; H, 6.51; N, 2.44. Found: C, 58.30; H, 6.39; N, 2.33.

After a solution of the imidate (974 mg, 1.7 mmol) in xylenes was refluxed for 14 h, the crude product was purified by silica gel column (hexane/EtOAc = 50:1) to give ***syn*-13d** in 86% yield (835 mg, 1.5 mmol). Colorless oil; $[\alpha]_D^{25}$ −22.9 (c = 1.0, $CHCl_3$); IR (neat) ν 3425, 3336, 3070, 1703, 822 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94–0.97 (6H, m), 1.02 (3H, d, J = 6.9 Hz), 1.07 (9H, s), 1.54–1.69 (3H, m), 2.84–2.88 (1H, m), 3.50 (1H, dd, J = 9.6, 6.4 Hz), 3.54 (1H, dd, J = 9.6, 5.9 Hz), 4.50–4.58 (1H, m), 4.84 (1H, dd, J = 38.0, 9.4 Hz), 6.69 (1H, d, J = 8.7 Hz), 7.38–7.46 (6H, m), 7.67 (4H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 19.3, 22.3, 22.4, 24.8, 26.8, 32.0 (d, J = 2.5 Hz), 40.8, 51.4 (d, J = 27.9 Hz), 68.1, 92.5, 111.6 (d, J = 13.6 Hz), 127.6, 129.6, 133.7, 133.7, 135.5, 135.6, 155.5 (d, J = 256.1 Hz), 161.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.2 (1F, dd, J = 38.0, 22.0 Hz); MS (ESI-TOF) m/z 572 $[M+H]^+$; HRMS calcd for $C_{28}H_{38}Cl_3FNO_2Si$ $[M+H]^+$: 572.1753, found: 572.1721.

4.5.4. N-((1R,4R,Z)-5-{[tert-Butyl(diphenyl)silyl]oxy}-2-fluoro-1-isobutyl-4-methyl-2-pentenyl)-2,2,2-tri- chloroacetamide anti-13d

According to the procedure for the preparation of ***syn*-13b**, (***Z*)-*anti*-12d** (567 mg, 1.3 mmol), DBU (0.40 ml, 2.6 mmol) and CCl_3CN (0.20 ml, 1.9 mmol) provided the imidate in 91% yield (674 mg, 1.2 mmol). Colorless oil; $[\alpha]_D^{25}$ −23.5 (c = 1.0, $CHCl_3$); IR (neat) ν 3344, 3072, 1664, 826 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, J = 2.7 Hz), 0.91 (3H, d, J = 2.7 Hz), 1.08 (9H, s), 1.12 (3H, d, J = 6.9 Hz), 1.63–1.68 (1H, m), 2.00–2.05 (2H, m), 2.29–2.39 (1H, m), 3.72 (1H, dd, J = 9.9, 3.5 Hz), 3.78 (1H, dd, J = 9.9, 5.1 Hz), 5.04 (1H, dt, J = 37.0, 7.8 Hz), 5.45 (1H, dd, J = 23.0, 9.4 Hz), 7.34–7.44 (6H, m), 7.64–7.68 (4H, m), 8.42 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 19.3, 22.1, 22.1, 26.9, 28.2, 32.4, 37.1, 64.4, 78.0 (d, J = 29.6 Hz), 91.6, 110.7 (d, J = 13.5 Hz), 127.6, 127.6, 129.6, 129.6, 133.6, 135.7, 154.3 (d, J = 256.6 Hz), 161.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.9 (1F, dd, J = 37.0, 23.0 Hz); MS (ESI-TOF) m/z 572 $[M+H]^+$; HRMS calcd for $C_{28}H_{38}Cl_3FNO_2Si$ $[M+H]^+$: 572.1714, found: 572.1721. Anal. Calcd for $C_{28}H_{37}Cl_3FNO_2Si$: C, 58.69; H, 6.51; N, 2.44. Found: C, 58.76; H, 6.58; N, 2.15.

After a solution of the imidate (1.2 g, 2.1 mmol) in xylenes was refluxed for 14 h, the crude product was purified by silica gel column (hexane/EtOAc = 50:1) to give ***anti*-13d** in 76% yield (912 mg, 1.6 mmol). Colorless oil; $[\alpha]_D^{25}$ +17.7 (c = 1.0, $CHCl_3$); IR (neat) ν 3427, 3338, 3071, 1705, 822 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (6H, d, J = 6.1 Hz), 1.01 (3H, d, J = 6.9 Hz), 1.04 (9H, s), 1.53–1.68 (3H, m), 2.81–2.88 (1H, m), 3.49 (1H, dd, J = 9.6, 6.2 Hz), 3.53 (1H, dd, J = 9.6, 6.1 Hz), 4.45–4.60 (1H, m), 4.76 (1H, dd, J = 38.0, 9.4 Hz), 6.54 (1H, d, J = 8.7 Hz), 7.36–7.44 (6H, m), 7.64–7.66 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 19.3, 22.4, 24.9, 26.8, 32.0, 40.9, 51.3 (d, J = 28.5 Hz), 67.9, 92.5, 111.3 (d, J = 13.5 Hz), 127.6, 129.6, 133.7, 135.6, 155.6 (d, J = 256.4 Hz), 161.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ–62.2 (1F, dd, J = 38.0, 21.0 Hz); MS (ESI-TOF) m/z 572 $[M+H]^+$; HRMS calcd for $C_{28}H_{38}Cl_3FNO_2Si$ $[M+H]^+$: 572.1721, found: 572.1738. Anal. Calcd for $C_{28}H_{37}Cl_3FNO_2Si$: C, 58.69; H, 6.51; N, 2.44. Found: C, 58.42; H, 6.36; N, 2.11.

4.6. General procedure for hydrolysis of trichloacetamide followed by N-Boc protection

A mixture of trichloacetamide **13** (4.5 mmol) and 5 M *aq.* NaOH (4.5 ml) in EtOH (9 ml) was stirred for 2 h at room temperature. Addition of water (5 ml) followed by extractive workup (EtOAc 20 ml × 3) and evaporation of the organic extracts under reduced pressure gave a crude residue. The residue dissolved in CH_2Cl_2 (25 ml) was treated with di-*tert*-butyl dicarbonate (5.5 mmol) and triethylamine (2.2 mmol) for 2 h at room temperature. Addition of water (5 ml) followed by extractive workup (EtOAc 20 ml × 3) and purification by silica gel column (hexane/EtOAc = 10:1) gave *N*-Boc derivative **19**.

4.6.1. tert-Butyl (2S,5R,Z)-6-{[tert-butyl(diphenyl)silyl]oxy}-3-fluoro-5-methyl-1-phenyl-hex-3-en-2-yl carbamate syn-19b

89% yield; colorless oil; $[\alpha]_D^{25}$ −3.3 (c = 1.0, $CHCl_3$); IR (neat) ν 3359, 3070, 1705, 824 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 1.03 (3H, d, J = 6.8 Hz), 1.09 (9H, s), 1.43 (9H, s), 2.79–2.80 (1H, m), 2.80–3.00 (2H, m), 3.28–3.37 (1H, m), 3.45 (1H, dd, J = 9.5, 5.3 Hz), 4.47 (1H, dd, J = 38.0, 9.5 Hz), 4.38–4.53 (1H, m), 4.72 (1H, brs), 7.12–7.19 (5H, m), 7.40–7.47 (6H, m), 7.66–7.70 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 19.3, 26.8, 28.3, 31.8 (d, J = 2.9 Hz), 38.9, 53.0 (d, J = 25.6 Hz), 67.9, 79.7, 109.8 (d, J = 13.2 Hz), 126.6, 127.6, 128.3, 129.4, 129.6, 133.9, 135.6, 136.7, 154.7, 156.3 (d, J = 254.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.1 (dd, J = 38.0, 19.0 Hz); MS (ESI-TOF) m/z 562 $[M+H]^+$; HRMS calcd for $C_{34}H_{45}FNO_3Si$ $[M+H]^+$: 562.3171, found: 562.3153.

4.6.2. tert-Butyl (2R,5R,Z)-6-{[tert-butyl(diphenyl)silyl]oxy}-3-fluoro-5-methyl-1-phenyl-hex-3-en-2-yl carbamate anti-19b

96% yield; colorless oil; $[\alpha]_D^{25}$ +8.7 (c = 1.0, $CHCl_3$); IR (neat) ν 3442, 3380, 2931, 1708, 825 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, d, J = 6.6 Hz), 1.18 (9H, s), 1.51 (9H, s), 2.90–2.93 (1H, m), 3.00 (2H, d, J = 6.9 Hz), 3.53–3.63 (2H, m), 4.48–4.60 (1H, m), 4.54

(1H, dd, J = 38.0, 9.3 Hz), 4.77 (1H, brs), 7.24–7.33 (5H, m), 7.45–7.52 (6H, m), 7.76–7.78 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 19.3, 26.8, 28.3, 31.8 (d, J = 2.9 Hz), 68.0, 79.7, 110.1 (d, J = 12.3 Hz), 126.6, 127.6, 128.3, 129.5, 133.8, 133.9, 135.6, 136.9, 154.7, 156.3 (d, J = 256.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.8 (1F, dd, J = 38.0, 18.0 Hz); MS (ESI-TOF) m/z 584 $[M+Na]^+$; HRMS calcd for $C_{34}H_{44}FNNaO_3Si$ $[M+Na]^+$: 584.2963, found: 584.2972. Anal. Calcd for $C_{34}H_{44}FNO_3Si$: C, 72.69; H, 7.89; N, 2.49. Found: C, 72.37; H, 7.68; N 2.34.

*4.6.3. tert-Butyl (1S,4R,Z)-5-{[tert-butyl(diphenyl)silyl]oxy}-2-fluoro-1-isobutyl-4-methylpent-2-enyl carbamate syn-***19d**

86% yield; colorless oil; $[\alpha]_D^{25}$ −20.9 (c = 1.0, $CHCl_3$); IR (neat) ν 3347, 2959, 1706, 823 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 0.91 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.6 Hz), 1.02 (3H, d, J = 6.8 Hz), 1.06 (9H, s), 1.35–1.50 (2H, m), 1.44 (9H, s), 1.61–1.66 (1H, m), 2.78–2.86 (1H, m), 3.49–3.56 (2H, m), 4.18 (1H, brs), 4.51 (1H, brs), 4.69 (1H, dd, J = 37.0, 9.2 Hz), 7.35–7.43 (6H, m), 7.66 (1H, brd); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 19.3, 22.4, 24.7, 26.8, 28.4, 31.8 (d, J = 2.7 Hz), 41.6, 50.4 (d, J = 27.3 Hz), 68.2, 79.5, 109.6 (d, J = 13.6 Hz), 127.6, 129.5, 133.8, 133.8, 135.6, 135.6, 155.0, 157.6 (d, J = 255.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.5 (1F, dd, J = 37.0, 22.0 Hz); MS (ESI-TOF) m/z 528 $[M+H]^+$; HRMS calcd for $C_{31}H_{47}FNO_3Si$ $[M+H]^+$: 528.3263, found: 528.3309. Anal. Calcd for $C_{31}H_{46}FNO_3Si$: C, 70.55; H, 8.78; N 2.65. Found: C, 70.28; H, 8.50; N 2.50.

*4.6.4. tert-Butyl (1R,4R,Z)-5-{[tert-butyl(diphenyl)silyl]oxy}-2-fluoro-1-isobutyl-4-methylpent-2-enyl carbamate anti-***19d**

71% yield; colorless oil; $[\alpha]_D^{25}$ +12.5 (c = 1.0, $CHCl_3$); IR (neat) ν 3408, 2960, 1709, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 0.92 (3H, d, J = 6.5 Hz), 0.93 (3H, d, J = 6.6 Hz), 0.95 (3H, d, J = 6.8 Hz), 1.07 (9H, s), 1.34–1.55 (2H, m), 1.43 (9H, s), 1.60–1.71 (1H, m), 2.78–2.89 (1H, m), 3.40–3.59 (2H, m), 4.19 (1H, brs), 4.50 (1H, brs), 4.64 (1H, dd, J = 38.0, 9.2 Hz), 7.35–7.43 (6H, m), 7.65–7.68 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 17.2, 19.3, 22.4, 22.6, 24.8, 26.8, 28.3, 31.8, 41.7, 50.3 (d, J = 28.3 Hz), 68.1, 79.4, 109.1 (d, J = 13.5 Hz), 127.6, 129.5, 133.8, 133.8, 135.6, 154.9, 157.9 (d, J = 258.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.2 (1F, dd, J = 38.0, 20.0 Hz); MS (ESI-TOF) m/z 528 $[M+H]^+$; HRMS calcd for $C_{31}H_{47}FNO_3Si$ $[M+H]^+$: 528.3337, found: 528.3309. Anal. Calcd for $C_{31}H_{46}FNO_3Si$: C, 70.55; H, 8.78; N 2.65. Found: C, 70.50; H, 8.94; N 2.58.

4.7. General procedure for Boc–AA–ψ[(Z)–CF = CH]–Ala–OH **14** *from* **19**

Desilylation: Treatment of *O*-silylated *N*-Boc derivative **19** (1.0 mmol) dissolved in THF (5 ml) with tetrabutylammonium fluoride (TBAF, 1.0 M solution in THF, 1.5 ml, 1.5 mmol) for 2 h at room temperature followed by extractive workup (EtOAc, 10 ml × 3) and purification by silica gel column (hexane/EtOAc = 3:1) gave the alcohol compound **20**.

Oxidation of alcohol **20** *to carboxylic acid* **14***:* To a solution of the alcohol **20** (0.5 mmol) in acetone (5 ml) was added Jones reagent dropwise until orange color was persisting and then the whole was stirred for 3 h at room temperature. The reaction mixture was stirred for further 15 min after the addition of 2-propanol (5 ml). Filtration of the precipitates with the aid of celite, the extractive workup of the filtrate (EtOAc, 20 ml × 3) and the subsequent purification by silica gel column (hexane/EtOAc = 3:1) gave the carboxylic acid **14**.

*4.7.1. (2R,5S,Z)-5-[(tert-Butoxycarbonyl)amino]-4-fluoro-2-methyl-6-phenylhex-3-enoic acid syn-***14b**

30% yield from ***syn*-19b**; colorless solid; $[\alpha]_D^{25}$ −24.0 (c 1.0, $CHCl_3$); IR (KBr) ν 3367, 2983, 1689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 1.26 (3H, d, J = 7.1 Hz), 1.41 (9H, s), 2.94 (2H, d, J = 6.9 Hz), 3.51–3.58 (1H, m), 4.43 (1H, brs), 4.66 (1H, d, J = 9.2 Hz), 4.78 (1H, dd, J = 36.0, 9.3 Hz), 7.15–7.30 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 17.7, 28.8, 34.9, 38.6, 52.6 (d, J = 24.9 Hz), 80.0, 106.0, 126.8, 128.4, 129.4, 136.3, 154.8, 157.7 (d, J = 253.3 Hz), 179.2; ^{19}F NMR (376 MHz, $CDCl_3$, 50 °C) δ −57.3 (1F, dd, J = 36.0, 16.0 Hz); MS (ESI-TOF) m/z 338 $[M+H]^+$; HRMS calcd for $C_{18}H_{25}FNO_4$ $[M+H]^+$: 338.1798, found: 338.1768. Anal. Calcd for $C_{18}H_{24}FNO_4$: C, 64.08; H, 7.17; N, 4.15. Found: C, 64.27; H, 7.22; N, 4.01.

*4.7.2. (2R,5R,Z)-5-[(tert-Butoxycarbonyl)amino]-4-fluoro-2-methyl-6-phenylhex-3-enoic acid anti-***14b**

29% yield from ***anti*-19b**; colorless solid; $[\alpha]_D^{25}$ −16.6 (c = 1.0, $CHCl_3$); IR (KBr) ν 3374, 2981, 1689, 823 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 1.17 (3H, d, J = 7.2 Hz), 1.41 (9H, s), 2.93 (2H, d, J = 7.1 Hz), 3.46–3.56 (1H, m), 4.43 (1H, brs), 4.69–4.80 (1H, m), 4.75 (1H, dd, J = 36.0, 9.3 Hz), 7.16–7.29 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 17.6, 28.3, 34.9 (d, J = 4.4 Hz), 38.6, 52.8 (d, J = 29.6 Hz), 65.8, 80.1, 106.2 (d, J = 12.4 Hz), 126.8, 128.4, 129.4, 136.4, 154.8, 157.5 (d, J = 256.5 Hz), 179.3; ^{19}F NMR (376 MHz, $CDCl_3$, 50 °C) δ −57.7 (1F, dd, J = 36.0, 17.0 Hz); MS (ESI-TOF) m/z 338 $[M+H]^+$; HRMS calcd for $C_{18}H_{25}FNO_4$ $[M+H]^+$: 338.1796, found: 338.1768. Anal. Calcd for $C_{18}H_{24}FNO_4$: C, 64.08; H, 7.17; N 4.15. Found: C, 64.07; H, 7.19; N 3.85.

*4.7.3. (2R,5S,Z)-5-[(tert-Butoxycarbonyl)amino]-4-fluoro-2,7-dimethyloct-3-enoic acid syn-***14d**

64% yield from ***syn*-19d**; colorless solid; $[\alpha]_D^{25}$ −62.2 (c = 1.0, $CHCl_3$); IR (KBr) ν 3363, 2979, 1693, 848 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 0.91 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.6 Hz), 1.30 (3H, d, J = 7.2 Hz), 1.41–1.53 (2H, m), 1.45 (9H, s), 1.63–1.68 (1H, m), 3.48–3.58 (1H, m), 4.20 (1H, brs), 4.62 (1H, brs), 4.94 (1H, dd, J = 36.0, 21.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 17.9, 22.4, 24.6, 28.3, 34.9, 41.3, 50.2 (d, J = 27.8 Hz), 79.8, 105.6, 155.0, 158.8 (d, J = 257.9 Hz), 179.7; ^{19}F NMR (376 MHz, $CDCl_3$, 50 °C) δ −59.7 (1F, dd, J = 36.0, 21.5 Hz); MS (ESI-TOF) m/z 326 $[M+Na]^+$; HRMS calcd for $C_{15}H_{26}FNNaO_4$ $[M+Na]^+$: 326.1746, found: 326.1744. Anal. Calcd for $C_{15}H_{26}FNO_4$: C, 59.39; H, 8.64; N 4.62. Found: C, 59.52; H, 8.35; N 4.48.

*4.7.4. (2R,5R,Z)-5-[(tert-Butoxycarbonyl)amino]-4-fluoro-2,7-dimethyloct-3-enoic acid anti-***14d**

79% yield from ***anti*-19d**. Colorless solid; $[\alpha]_D^{25}$ −27.0 (c = 1.0, $CHCl_3$); IR (KBr) ν 3251, 3112, 2962, 1716, 833 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 0.94 (6H, d, J = 6.6 Hz), 1.30 (3H, d, J = 7.2 Hz), 1.39–1.56 (2H, m), 1.45 (9H, s), 1.63–1.70 (1H, m), 3.51–3.59 (1H, m), 4.20 (1H, brs), 4.61 (1H, brs), 4.95 (1H, dd, J = 36.0, 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 18.3, 22.7, 22.9, 25.2, 28.7, 35.4 (d, J = 4.4 Hz), 41.8, 50.4 (d, J = 27.4 Hz), 80.3, 105.5 (d, J = 12.8 Hz), 155.4, 159.6 (d, J = 260.4 Hz), 179.9; ^{19}F NMR (376 MHz, $CDCl_3$, 50 °C) δ −58.1 (1F, dd, J = 36.0, 19.0 Hz); MS (ESI-TOF) m/z 304 $[M+H]^+$; HRMS calcd for $C_{15}H_{27}FNO_4$ $[M+H]^+$: 304.1930, found: 304.1924. Anal. Calcd for $C_{15}H_{26}FNO_4$: C, 59.39; H, 8.64; N 4.62. Found: C, 59.31; H, 8.63; N 4.61.

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