Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 5741–5753

Stereoselective synthesis of (*Z*)-fluoroalkenes directed to peptide isosteres: copper mediated reaction of trialkylaluminum with 4,4-difluoro-5-hydroxyallylic alcohol derivatives

Yuko Nakamura,[a] Midori Okada,[a] Azusa Sato,[a] Hiroaki Horikawa,[a] Minoru Koura,[b] Akio Saito[b] and Takeo Taguchi[b,*]

[a]*Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan*
[b]*Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan*

Received 26 March 2005; revised 16 April 2005; accepted 18 April 2005

Abstract—Copper mediated alkyl-transfer reaction of trialkylaluminum (R_3Al) with (*E*)-4,4-difluoro-5-hydroxyallylic alcohol derivative smoothly proceeded to give the corresponding 2-alkylated 4-fluoro-5-hydroxyhomoallylic alcohol derivative with completely *Z* and 2,5-*syn* selective manner. Regio- and stereoselective conversion of the C5-hydroxyl group of the fluoroolefin thus obtained to amino group could be achieved through one-pot mesylation and azidation reaction.

1. Introduction

Fluoroolefin (–CF═CH–) is considered to be an ideal mimic for an amide bond (–CO–NH–) due to the close similarities of the steric and electronic properties.[1] Contrary to these similarities, fluoroolefin should be a non-hydrolyzable bond both chemically and enzymatically, and the lack of rotational freedom of this bond is also a different property from that of amide bond. On the basis of these unique properties, utilization of (*Z*)-fluoroalkene dipeptide or depsipeptide isosteres as non-hydrolyzable and/or conformationally restricted replacements for the parent amide bonds has attracted much attention in the field of medicinal chemistry (Fig. 1).[2–6]

Each of such fluoroalkene-modified dipeptide and depsipeptide isosteres has a set of eight stereoisomers due to two chiral carbon atoms (C2 and C5) and *E*/*Z* configuration of olefin part in the molecule. In Figure 1, a typical dipeptide L-AA_1-L-AA_2 consisting of two L-amino acids, a part of a depsipeptide D-OA_1-L-AA_2 derived from D-oxy acid and L-amino acid, and the corresponding fluoroalkene isosteres are depicted.

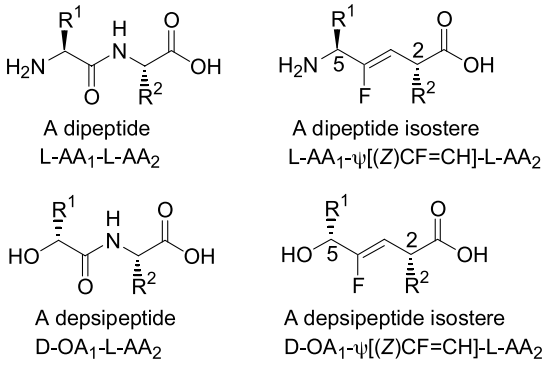
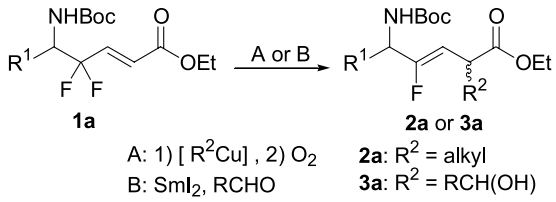


Figure 1. Replacement of amide bond by *Z*-fluoroolefin.

To develop synthetic methods for these fluoroalkene isosteres, stereochemical control of the olefin-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. Furthermore, the use of readily obtainable starting material is also important. So far, extensive efforts to develop highly stereoselective methods for functionalized fluoroolefinic compounds have been reported.[7–15] For example, directed to the preparation of fluoroalkene dipeptide isosteres, Fujii and Otaka et al. recently demonstrated two types of defluorinative reactions using γ,γ-difluoro-α,β-enoate derivatives **1a** as the starting material. That is, the difluoro enoates **1a** having amino group at δ-position could be converted to the dipeptide

Keywords: Fluoroalkene; Difluoroallylic alcohol; Trialkylaluminum; Cuprous iodide; Peptide isosteres.
* Corresponding author. Tel./fax: +81 426 76 3257;
e-mail: taguchi@ps.toyaku.ac.jp

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.04.034



Scheme 1.

isostere form **2a** by utilizing organocopper reagent under reductive–oxidative alkylation conditions (Scheme 1, A).[16] Furthermore, they also reported samarium diiodide (SmI_2)-mediated reduction of **1a** followed by the reaction with carbonyl compounds to give α-substituted fluoroalkenoates **3a** (Scheme 1, B).[17] Although these reactions proceeded with complete *Z*-selectivity, low diastereoselectivity remained as a future subject to be solved.

Independently, we have also reported that using the similar difluoro enoate derivatives **1b–d**, α-alkylated (*Z*)-γ-fluoro-β,γ-enoate **2** can be synthesized upon treating with trialkylaluminum (R_3Al) in the presence of Cu(I) or through lithiocuprate (Me_2CuLi) mediated reductive defluorination followed by regioselective α-alkylation with alkyl halide (Scheme 2, Eqs. 1 and 3).[18] In the lithiocuprate reaction, reductive defluorination product **4** was obtained by quenching with H_2O instead of alkyl halide (Scheme 2, Eq. 2).

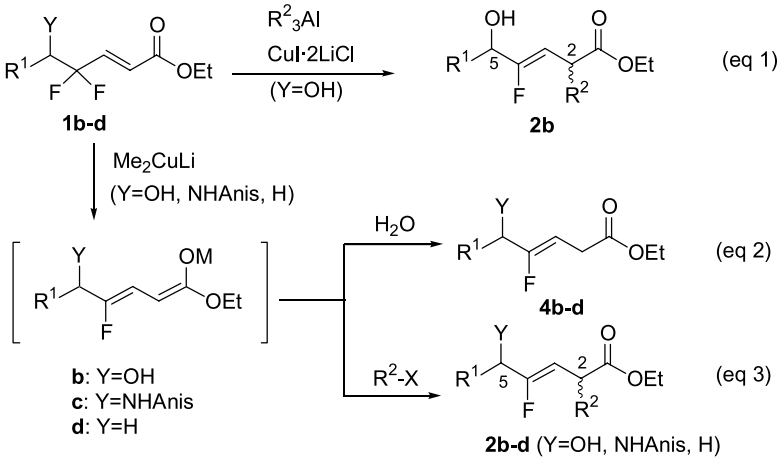
Although these reactions proceeded in excellent *Z*-selectivity, synthetically useful level of diastereo-control could not be realized. Further efforts were made to develop a highly diastereoselective preparation of these compounds. We found that Cu(I)-mediated alkyl-transfer reaction of trialkylaluminum (R_3Al) with (*E*)-4,4-difluoro-5-hydroxyallylic alcohol derivatives *E*-**5** provided the corresponding 2-alkylated 4-fluorohomoallylic alcohol derivatives **6** in completely *Z*- and 2,5-*syn*-selective manner.[19] Furthermore, regio- and stereoselective conversion of the secondary chiral hydroxyl group in the difluoroallylic alcohol **7** into amino functionality could be achieved through one-pot mesylation and azidation protocol (Scheme 3). In this paper, we report these promising results directed to the stereocontrolled preparation of (*Z*)-fluoroalkene depsipeptide or dipeptide isosteres in detail.

2. Results and discussion

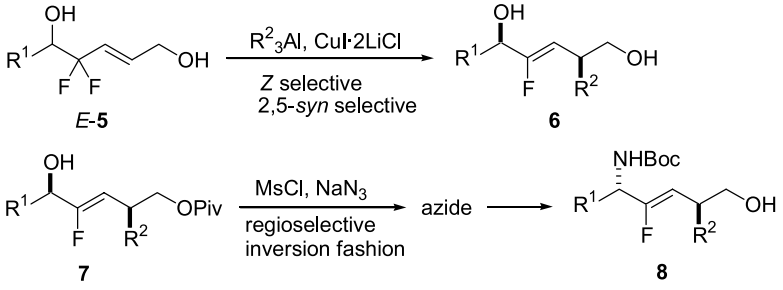
2.1. Reaction with lithiocuprate

First, we examined the reactivity and stereoselectivity in the reaction of (*E*)-4,4-difluoro-5-hydroxyallylic alcohol derivatives **5a**, **5b** with a copper reagent derived from alkyllithium, typically such as Gilman reagent (Table 1).[19]

Contrary to the case of ester derivative **1b** (Y=OH) which provided the reductive defluorination product **4b** rather than expected 2-methylated product **2b** (Y=OH, R^2=Me) as shown in Scheme 2, the reaction of these alcohol derivatives **5a**, **5b** with dialkylcopper lithium R_2CuLi proceeded in SN2′ manner giving rise to 2-alkylated homoallylic alcohol

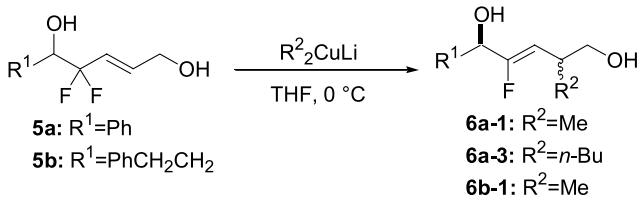


Scheme 2.



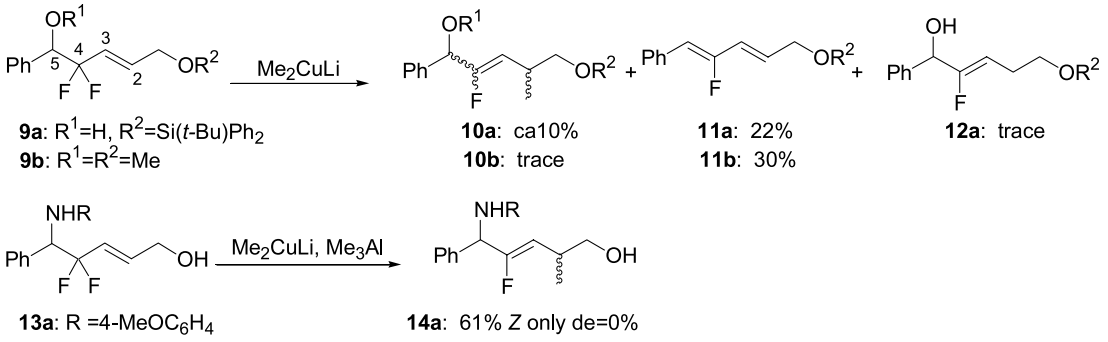
Scheme 3.

Table 1. Reaction of (*E*)-4,4-difluoro-5-hydroxyallylic alcohol with R_2CuLi



Entry	5	Reagent	Additive	R^2	6	Yield (%)[a]	*Z*/*E*[b]	*syn*/*anti*[c]
1	**5a**	Me_2CuLi	—	Me	**6a-1**	90	15	2:1
2		Me_2CuLi	Me_3Al	Me	**6a-1**	88	>95	95:1
3		*n*-Bu_2CuLi	Me_3Al	*n*-Bu	**6a-3**	58	13	1.1:1[d]
4	**5b**	Me_2CuLi	Me_3Al	Me	**6b-1**	90	11	1.1:1[d]

[a] Isolated yield.
[b] Determined by ^1H NMR.
[c] Ratio for *Z* isomer.
[d] Relative stereochemistry was not determined.

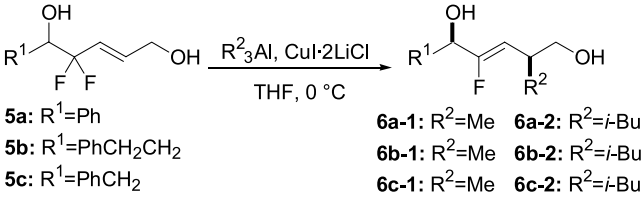


Scheme 4.

derivatives **6a**, **6b**.[20] For example, by treating **5a** with Me_2CuLi (5 equiv) in THF at 0 °C for 2.5 h, 2-methylated homoallylic alcohol **6a-1** was obtained in 90% yield with relatively high *Z* selectivity (*Z*/*E*=15), but with low diastereoselectivity (*syn*/*anti*=2 for *Z* isomer) (entry 1). While limited to the case of phenyl derivative **5a** and Me_2CuLi, a remarkable improvement in diastereroselectivity was observed by the addition of Me_3Al (entry 2). However, the additive effect of Me_3Al on the stereoselectivity was not observed in the reaction of **5a** with *n*-Bu_2CuLi instead of Me_2CuLi or alkyl (β-phenylethyl) derivative **5b** with Me_2CuLi (entries 3 and 4).

Reactions of lithiocuprate with some structure modified substrates were also examined. It was found that both allylic alcohol structure and C5-hydroxyl group may be important

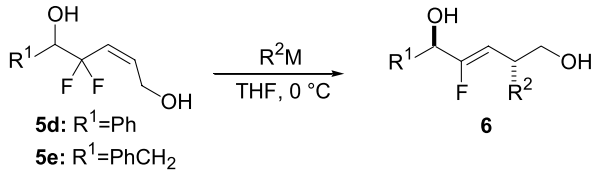
Table 2. Cu(I)-mediated reaction of (*E*)-4,4-difluoro-5-hydroxyallylic alcohol with R_3Al



Entry	5	Reagent	R^2	6	Yield (%)[a]	*Z*/*E*[b]	*syn*/*anti*[c]
1	**5a**	Me_3Al	Me	—	0[d]	—	—
2		Me_3Al, CuI·2LiCl	Me	**6a-1**	77	>95	>95:<1
3		*i*-Bu_3Al, CuI·2LiCl	*i*-Bu	**6a-2**	68	>95	>95:<1
4	**5b**	Me_3Al, CuI·2LiCl	Me	**6b-1**	65	>95	>95:<1
5		*i*-Bu_3Al, CuI·2LiCl	*i*-Bu	**6b-2**	66	>95	>95:<1
6	**5c**	Me_3Al, CuI·2LiCl	Me	**6c-1**	98	>95	>95:<1
7		*i*-Bu_3Al, CuI·2LiCl	*i*-Bu	**6c-2**	78	>95	>95:<1

[a] Isolated yield.
[b] Determined by ^1H NMR.
[c] Ratio for *Z* isomer.
[d] Without CuI·2LiCl, **5a** was recovered in 90%.

Table 3. Alkyl-transfer reaction of (*Z*)-4,4-difluoro-5-hydroxyallylic alcohol



Entry	5	Reagent	Time (h)	R^2	6	Yield (%)[a]	*syn/anti*[b,c]	5 (%)[b,d]
1	**5d**	Me_3Al, CuI·2LiCl	22	Me	**6a-1**	52	1:10.5	41
2		*i*-Bu_3Al, CuI·2LiCl	22	*i*-Bu	**6a-2**	23	1:5.8	60
3		Me_2CuLi	4	Me	**6a-1**	76	1:4.7	—
4	**5e**	*i*-Bu_3Al, CuI·2LiCl	22	*i*-Bu	**6c-2**	32	1:2.9	32
5		Me_2CuLi	4	Me	**6c-1**	89	1:2.0[e]	—

[a] Isolated yield.
[b] Determined by ^1H and ^{19}F NMR.
[c] Ratio for *Z*-isomer is shown.
[d] Recovery of **5**.
[e] *Z*/*E* ratio of **6c-1** was 15:1.

for clean reaction, since the silylation of the primary hydroxyl group (substrate **9a**) or methylation of both hydroxyl groups (substrate **9b**) gave the 2-methylated product **10** as a mixture of *Z*/*E* and *syn*/*anti* isomers along with the formation of the diene compound **11**. In the case of **9a**, reductive defluorination compound **12a** was also detected. With C5-amino substrate **13a**, reaction proceeded in completely non-diastereoselective manner to give the 2-methylated (*Z*)-fluoroalkene compound **14a** in 61% yield (Scheme 4). From these results, a high level of stereocontrol could not be achieved by lithiocuprate reactions.

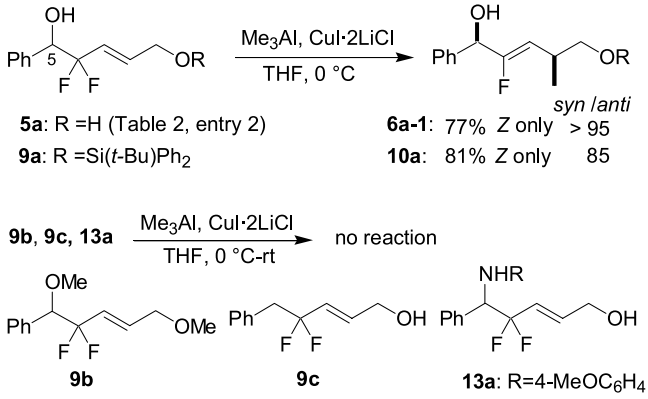
2.2. Reaction with trialkylaluminum in the presence of CuI·2LiCl

Contrary to the low diastereoselectivity in the reaction with lithiocuprate, when the reaction of (*E*)-difluoroallylic alcohols **5a**–**5c** were conducted using a combination of trialkylaluminum (R_3Al, 5–10 equiv) and CuI·2LiCl[21] (2.5 equiv) in THF at 0 °C for 15–22 h, the desired 2-alkylated 4-fluorohomoallylic alcohols **6a**–**6c** were obtained in good to excellent yields (62–98%) with complete *Z*- and 2,5-*syn* selectivity (Table 2, entries 2–7).[19]

In the absence of CuI·2LiCl, no reaction occurred upon treating **5a** with Me_3Al to result in the recovery of **5a** (Table 2, entry 1). Thus, Cu(I) is a crucial additive for the present alkyl-transfer reaction of trialkylaluminum to proceed,[22,23] possibly through the Al–Cu transmetalation and activation of fluorine atom as a leaving group by aluminum–fluorine interaction (see mechanistic discussion).[24,25] As shown in Table 2, with either phenyl or alkyl (phenethyl and benzyl) substituted derivatives, not only methyl but also longer alkyl (*iso*-butyl) aluminum reagent gave the satisfactory results. Thus, we could provide a highly general and stereocontrolled method for 2-alkylated (*Z*)-2,5-*syn*-4-fluoro-5-hydroxy-3-alkenols **6** from *E*-isomer of difluoroallylic alcohols **5**.

Next, the reactivity of *Z*-isomer of difluoroallylic alcohols **5d**, **5e** and their stereochemical outcome were compared with those of *E*-isomers **5a**, **5c**. The results are shown in Table 3. The reaction of *Z*-isomer **5d** under the similar conditions (Me_3Al, CuI·2LiCl, THF, 0 °C, 22 h) proceeded more slowly than that of *E*-isomer **5a** to give the 2-methylated 4-fluorohomoallylic alcohol **6a-1** in moderate yield (52%) along with the recovery of **5d** (41%) (entry 1). The stereochemistry of the product **6a-1** thus obtained indicated that the reaction proceeded in highly *Z*-selective manner (*Z*/*E* = > 95) and in relatively highly *anti*-selective manner (*syn*/*anti* = 1/10.5) opposite to that of *E*-isomer **5a**. Using *i*-Bu_3Al instead of Me_3Al under the similar conditions, the reaction of **5d**, **5e** gave the desired products **6a-2**, **6c-2** in low yields along with the recovery of **5d**, **5e**, respectively (entries 2 and 4). In these cases complete *Z*-selectivity and moderate 2,5-*anti* selectivity were also observed. On the other hand, as shown in entries 3 and 5, the reaction of *Z*-isomers **5d**, **5e** with lithiocuprate Me_2CuLi proceeded smoothly to give **6a-1**, **6c-1** in good yields (76 and 89%, respectively), but with lower diastereoselectivity (*syn*/*anti* = 1/4.7 for **6a-1** and 1/2.0 for **6c-1**). Although the product yield should be improved in the case of *Z*-isomer of difluoroallylic alcohols **5d**, **5e**, the results mentioned above indicated that both *syn*- and *anti*-isomer of 2-alkylated (*Z*)-4-fluoro-5-hydroxyhomoallylic alcohols **6** are stereoselectively constructed by the reaction with R_3Al and CuI·2LiCl.

Next, to see the substrate specificity of the present Cu(I)-mediated alkyl-transfer reaction of trialkylaluminum with



Scheme 5.

4,4-difluoroallylic alcohol derivatives and for mechanistic consideration about the excellent stereoselectivity observed in the reaction with (*E*)-isomer of 5-hydroxyl derivatives **5** (see Table 2), we examined similar reactions using various structure-modified substrates (Scheme 5).

First, the reaction of the substrate **9a** prepared by silylation of the primary hydroxyl group of **5a** was examined to see the effect of allylic alcohol structure on the reactivity. This substrate **9a** showed similar reactivity to that of non-protected substrate **5a** to give the 2-methylated product **10a** in 81% yield with an excellent *Z*-selectivity and high 2,5-*syn* selectivity. On the other hand, etherification of both hydroxyl groups (substrate **9b**) and removal of C5-hydroxyl group (substrate **9c**) resulted in complete recovery of these substrates upon treating with Me_3Al and CuI·2LiCl in THF. Moreover, replacement of C5-hydroxyl group by an amino group such as 4-methoxyanilino derivative **13a** also led to the recovery of the starting material. From these results, it was clearly demonstrated that the free hydroxyl group at 5-position should be essential for the Cu(I)-mediated alkyl-transfer reaction of trialkylaluminum, while the allylic alcohol structure is not always required.

2.3. Mechanism

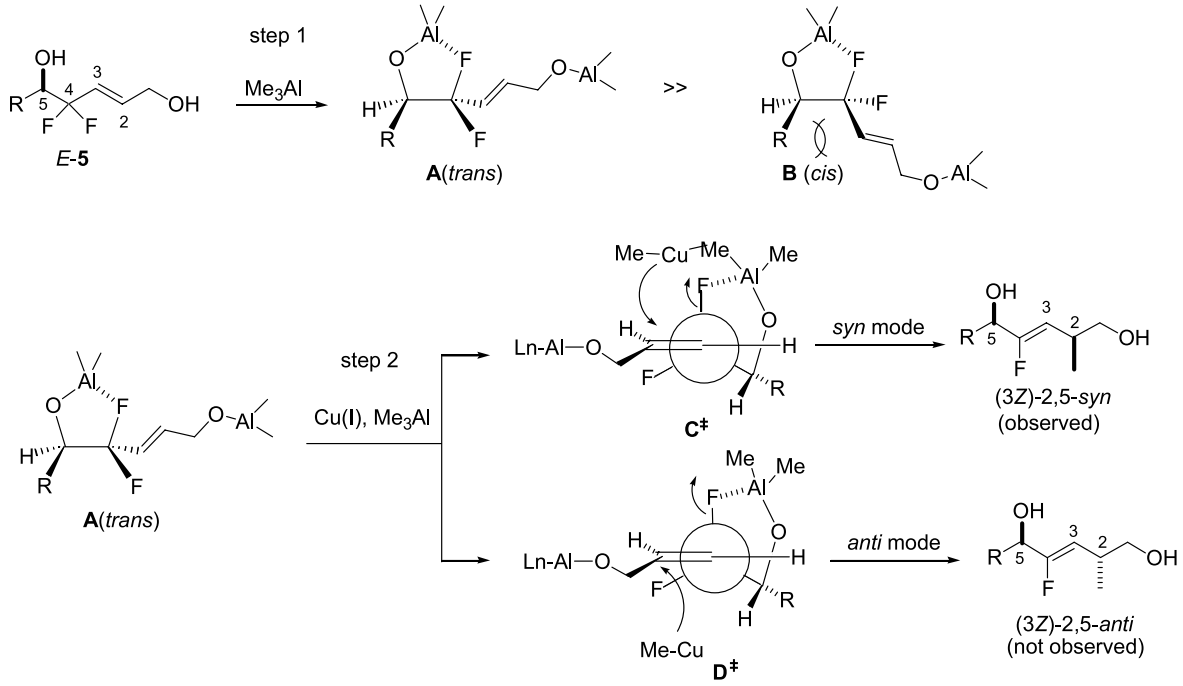
Although mechanistic detail is not clear at this moment, the above mentioned alkyl-transfer reaction may involve Al–Cu transmetalation and activation of fluorine atom as a leaving group through fluorine–aluminum coordination.

As such examples of copper-mediated alkyl-transfer reactions of alkylaluminum were reported conjugate addition with α,β-enones[22] and allylic substitution with allylic phosphates and halides.[23] Similar to these reactions, we believe that the present defluorinative allylic alkylation of difluoroallylic alcohol **5** with trialkylaluminum should involve Al–Cu transmetalation since without Cu(I) no reaction occurred. Furthermore, on the basis of absolutely essential functionality of the C5-hydroxyl group in the substrate **5** as shown in Scheme 5 and relatively strong fluorine–aluminum coordination,[24,25] it would be expected that activation of fluorine atom as a leaving group can be gained by the formation of a five-membered complex **A** easily formed when the substrate **5** is mixed with trialkylaluminum. Due to the steric reason, the complex **A** which is *trans* isomer with respect to the relative stereochemistry between propenyl moiety and R substituent may be more favorable as compared with complex **B**, the corresponding *cis* isomer (Scheme 6, step 1).

Next, we analyzed alkyl-transfer process on the assumption that in the complex form **A** the fluorine atom coordinating to aluminum acts as a leaving group[24] and the reaction proceeds via oxidative addition of aluminocuprate formed by Al–Cu transmetalation.

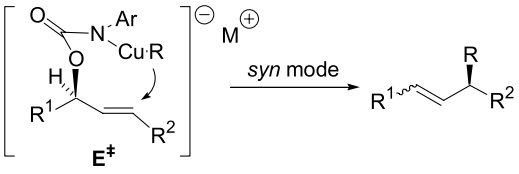
From the accumulated data, the copper-mediated allylic alkylation reactions proceed through either *anti* or *syn* to the leaving group depending on the type of leaving group, nature of organometallics used and sometimes on the additive.[26–30] In our reaction using *E* isomer of 4,4-difluoroallylic alcohol *E*-**5**, when the oxidative addition of methylcopper occurs from *anti* to the leaving fluorine atom as shown in the model $\mathbf{D}^{\ddagger}$, the stereochemistry of the product should be 3*Z* and 2,5-*anti*, although the observed stereochemistry was 2,5-*syn*. Alternatively, if we consider the *syn*-addition of copper to the leaving group through an intramolecular process of the aluminocuprate as shown in the model $\mathbf{C}^{\ddagger}$, the expected stereochemistry of the product is essentially identical with the observed (3*Z*)-2,5-*syn* stereochemistry (Scheme 6, step 2).

This intramolecular process may be similar to the *syn* allylic



Scheme 6. Mechanism for (3*Z*)-2,5-*syn* selectivity with *E*-**5**.

substitution reaction with allylic NH-carbamate derivatives, in which the carbamate anion acts as a ligand onto the alkylcopper species to form the ate complex as shown in the model **E**‡, thereby the alkyl-transfer reaction occurs intramolecularly in *syn* selective manner (Scheme 7).[28] Likewise, in the model **C**‡, methyl group on the aluminum coordinated by the fluorine atom possibly acts as a ligand onto methyl copper to form aluminocuprate ate complex (Scheme 6).



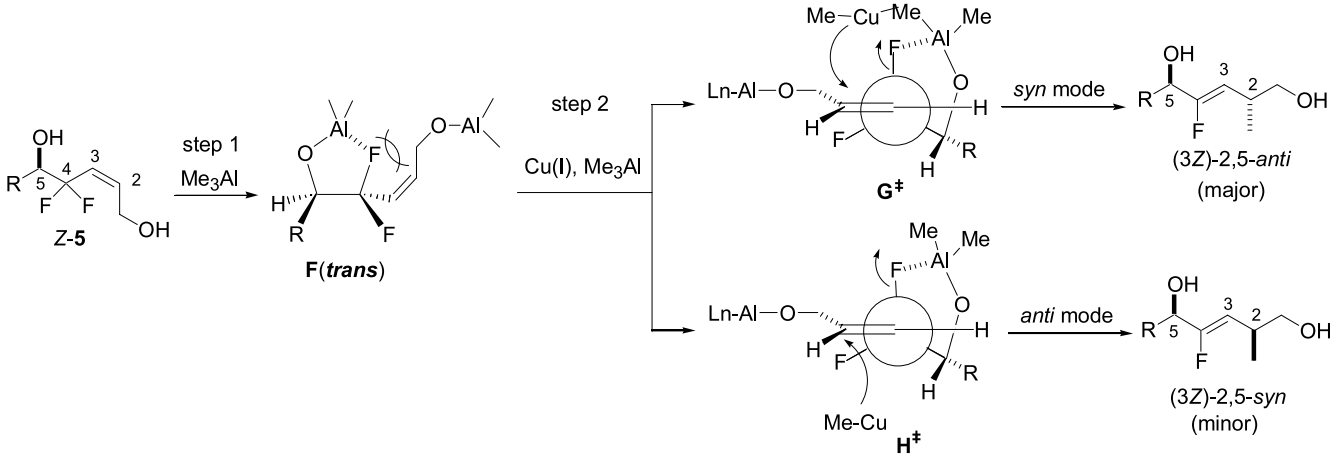
Scheme 7. *syn*-Allylic substitution of NH-carbamate with alkylcuprate.

Contrary to the *E* isomer of the substrate *E*-**5**, in the case of *Z* isomer *Z*-**5**, which showed lower reactivity and moderate 2,5-*anti* selectivity in the product (see Table 3), the five-membered complex form **F** would be more unstable as compared with the complex form **A** due to the unfavorable steric interaction between C1 and C4 (fully substituted carbon atom) in the complex **F**, thereby the reaction of *Z*-**5** showed lower reactivity. Furthermore, as a possible explanation for the moderate 2,5-*anti* selectivity, while the intramolecular alkyl transfer through the model **G**‡ provides the major 2,5-*anti* product, competitive intermolecular oxidative *anti*-addition of methylcopper to the fluorine atom coordinating to aluminum as shown in the model **H**‡ would be a reaction pathway for 2,5-*syn* product (Scheme 8).

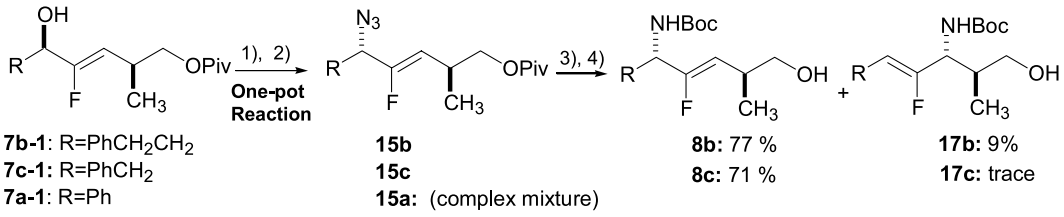
2.4. Conversion of chiral fluoroallylic alcohol to *N*-Boc amino derivative

As mentioned above, towards to the direct production of peptide isostere the present Cu(I)-mediated alkyl-transfer reaction could not be applicable to the substrate having amino group at 5-position (see Scheme 5, **13a**). Therefore, we examined the regio- and stereoselective conversion of C5-hydroxyl group to amino group using the above mentioned fluoroallylic alcohol derivative **6** prepared in completely stereoselective manner (Table 2). In a literature, although the substitution reaction of the primary hydroxyl group of fluoroallylic alcohols by the Mitsunobu reaction (Ph_3P, DEAD, phthalimide) proceeded smoothly,[3,4] those of secondary allylic alcohols seem to be difficult due to the low reactivity.[1e,2a,16a] Similar tendency was also observed in our case. That is, the Mitsunobu reactions of the pivaloyl ester derivative **7b**-**1**, **7c**-**1** were conducted, but these were not fruitful to result in only recovery of the starting materials.

We also examined stepwise procedure involving sulfonylation of the hydroxyl group followed by the subsequent substitution reaction with sodium azide or benzylamine under various reaction conditions. Most of these experiments resulted in a messy mixture due to the instability of these allylic sulfonates. While such a problematic event in allylic substitution reaction is quite common, there have been some successful examples reported so far.[31,32] For example, by one-pot reaction of mesylation of hydroxyl group in the presence of large excess amount of sodium azide, a clean SN2 replacement of an optically pure benzylic hydroxyl group (5,6,7,8-tetrahydroisoquinolin*E*-8-ol or benzhydrol derivative) was reported.[33,34] Similar one-pot operation was found to work very nicely with our fluoroallylic alcohol derivatives **7b**-**1**, **7c**-**1**. Thus, after a mixture of the alcohol **7b**-**1**, dimethylaminopyridine (DMAP, 3 equiv) and sodium azide (20 equiv) suspended in CH_2Cl_2 was treated with methanesulfonyl chloride (3 equiv) for 30 min at room temperature, a clear solution by the addition of DMSO was further stirred for 3 h at the same temperature giving rise to the desired 5-azide derivative **15b** in high yield. Since the rearrangement of the allylic azide forming 3-azide isomer seemed to easily occur, conversion of the azide **15b** to *N*-Boc-protected amino derivative **8b** was carried out immediately after azidation reaction, while we obtained the desired **8b** along with the formation of rearranged isomer **17b** as a by-product. Thus, by treatment of crude **15b** with $LiAlH_4$ followed by with di-*t*-butyl dicarbonate and triethylamine we obtained **8b** and **17b** in 77% and 9% yield, respectively. The 2,5-*anti* stereochemistry was unambiguously confirmed by X-ray analysis of **8b** indicating that the present one-pot azidation reaction proceeded in a complete inversion



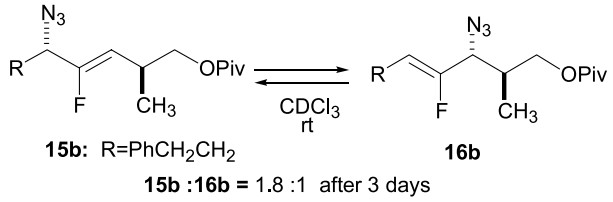
Scheme 8. Mechanism for (3*Z*)-2,5-*anti* selectivity with *Z*-**5**.



Scheme 9. Reagent and conditions: (1) DMAP (3 equiv), NaN_3 (20 equiv), MsCl (3 equiv), CH_2Cl_2, rt, 30 min; (2) DMSO, rt, 3 h; (3) $LiAlH_4$, THF, 1.5 h; (4) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 30 min.

fashion. Similar stereoselective conversion from **7c-1** to **8c** was also achieved (Scheme 9). However, under the similar reaction conditions the benzylic alcohol derivative **7a-1** (R=Ph) gave a complex mixture, possibly due to the highly labile nature of the corresponding mesylate.

It should be noted that fluoroallylic azide **15b**, **15c** thus obtained slowly isomerize to 3-azide derivatives.[32,35] Thus, when a solution of 5-azide **15b** in $CDCl_3$ was left at room temperature for 3 days, **15b** changed to a mixture of **15b** and the 3-azide isomer **16b** in a ratio of 1.8:1 (Scheme 10).



Scheme 10.

3. Conclusion

In conclusion, we have established a stereoselective (completely *Z* and 2,5-*syn* selective) synthesis of 5-hydroxylated 2-alkyl-4-fluoro-3-alkene-1-ol derivatives through the defluorinative allylic substitution reaction of difluoroallylic alcohol derivatives with trialkylaluminum and Cu(I). Furthermore, a high yield and complete inversive conversion of C5-hydroxyl group of these stereoselectively synthesized fluoroallylic alcohol derivatives to amino group could be achieved through one-pot preparation of azide compound. The present reaction should provide an efficient method for the preparation of functionalized *Z*-fluoroolefins, which, in particular, are applicable to the preparation of depsipeptide isosteres and dipeptide isosteres.

4. Experimental

4.1. General

Trimethylaluminum (1.0 M in hexane) and triisobutylaluminum (1.0 M in hexane) are available commercially. All reactions were conducted under an argon atmosphere. ^1H and ^{13}C NMR spectra were measured at 400 and 100 MHz in $CDCl_3$, and the chemical shifts are given in ppm using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^1H NMR and $CDCl_3$ (77.01 ppm) for ^{13}C NMR as an internal standard, respectively. ^{19}F NMR spectra were measured at 376.5 MHz and the chemical shifts are given in ppm using benzotrifluoride (0 ppm) as an internal standard. Mass spectra and HRMS were recorded by EI or ESI methods. Column chromatography was performed on silica gel (70–230 mesh). Medium-pressure liquid chromatography (MPLC) was performed on a 30 cm×2.2 cm i.d. prepacked column (silica gel, 50 μm) with a UV or RI detector.

4.2. Preparation of 5-substituted (*E*)-4,4-difluoro-2-pentene-1,5-diol (5)

A mixture of ethyl ester of 5-substituted (*E*)-4,4-difluoro-5-hydroxy-2-pentenoic acid[17] (5 mmol) and DIBAL (1 M hexane solution, 15 mmol) in THF was stirred at −70 °C for 30 min. The reaction mixture was quenched with 5% HCl and extracted with AcOEt. The combined organic layer was dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography to give *E*-**5**.

4.2.1. (*E*)-4,4-Difluoro-5-phenyl-2-pentene-1,5-diol (5a). Quant. Colorless oil. IR ($CHCl_3$) ν cm^{-1}; 3622, 3150–3600, 2902, 1683. ^1H NMR (400 MHz, $CDCl_3$) δ; 2.66 (1H, brs), 3.62 (1H, brs), 4.10 (2H, s), 4.84 (1H, t, J=9.6 Hz), 5.73–5.85 (1H, m), 6.07–6.17 (1H, m), 7.26–7.43 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 61.6, 75.8 (t, J=30.5 Hz), 119.7 (t, J=244.3 Hz), 121.5 (t, J=25.4 Hz), 127.7, 128.2, 128.7, 136.2 (d, J=2.7 Hz), 136.6 (t, J=8.2 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −41.61 (1F, d, J=247 Hz), −45.09 (1F, dt, J=247, 11 Hz). EI-MS *m/z*; 196 (M^+-H_2O), 177, 107. HRMS; calcd for $C_{11}H_{10}F_2O$ (M^+-H_2O): 196.0700. Found: 196.0712.

4.2.2. (*E*)-4,4-Difluoro-7-phenyl-2-heptene-1,5-diol (5b). 61% yield. Colorless oil. IR ($CHCl_3$) ν cm^{-1}; 3622, 2932, 2866, 1683. ^1H NMR (400 MHz, $CDCl_3$) δ; 1.70–1.84 (1H, m), 1.90–2.04 (1H, m), 2.60–2.74 (1H, m), 2.84–2.96 (1H, m), 3.45 (1H, s), 3.69 (1H, s), 3.74 (1H, m), 4.20 (2H, s), 5.80–5.96 (1H, m), 6.18–6.30 (1H, m), 7.21–7.32 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 31.5, 61.5, 72.7 (t, J=30.2 Hz), 120.5 (t, J=243.3 Hz), 121.6 (t, J=25.6 Hz), 126.0, 128.4, 136.1 (t, J=8.4 Hz), 141.1. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −42.42 (1F, d, J=248 Hz), −47.98 (1F, d, J=248 Hz). EI-MS *m/z*; 242 (M^+), 224 (M^+-H_2O), 206, 117. HRMS; calcd for $C_{13}H_{16}F_2O_2$ (M^+): 242.1118. Found: 242.1104.

4.2.3. (*E*)-4,4-Difluoro-6-phenyl-2-hexene-1,5-diol (5c). 97% yield. Colorless oil. IR ($CHCl_3$) ν cm^{-1}; 3620, 3460, 2924, 1732, 1682. ^1H NMR (400 MHz, $CDCl_3$) δ; 2.58 (1H, brs), 2.69 (1H, dd, J=14.2, 10.4 Hz), 2.90 (1H, d, J=8.0 Hz), 3.03 (1H, dd, J=14.2, 2.4 Hz), 3.98 (1H, m), 4.23 (2H, s), 5.92–5.96 (1H, m), 6.29–6.34 (1H, m),

7.24–7.36 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 36.44, 61.65, 74.62 (t, J=30.3 Hz), 120.18 (t, J=243.5 Hz), 121.64 (t, J=25.4 Hz), 126.69, 128.53, 129.35, 136.34 (t, J=8.4 Hz), 137.31. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −42.38 (1F, d, J=249 Hz), −48.46 (1F, dt, J=249, 12 Hz). EI-MS m/z; 228 (M^+), 210 (M^+-H_2O), 190, 121. HRMS; calcd for $C_{12}H_{14}F_2O_2$ (M^+): 228.0962. Found: 228.0954.

4.2.4. (*Z*)-4,4-Difluoro-5-phenyl-2-pentene-1,5-diol (5d). To a suspension of 5% Pd–$BaSO_4$ (183 mg, 0.54 mmol) in MeOH (5 ml) was added dropwise quinoline (183 mg, 1.42 mmol) in MeOH (5 ml) at 0 °C and the mixture was stirred at room temperature for 15 min. To this mixture was added 5-{[*tert*-butyl(diphenyl)silyl]oxy}-2,2-difluoro-1-phenyl-3-pentyn-1-ol[36] (1.971 g, 4.38 mmol) in DMF (5 ml) at room temperature and then under a hydrogen atmosphere the mixture was stirred at room temperature for 4 h. The reaction mixture was filtrated through celite pad with the aid of AcOEt. The combined filtrate was diluted with water and extracted with AcOEt. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography [hexane/AcOEt (5:1)] to give TBDPS-**5d** (1.851 g, 93% yield). After a mixture of TBDPS-**5d** (358 mg, 0.79 mmol) and TBAF (1 M THF solution, 0.5 ml, 0.5 mmol) in THF (5 ml) was stirred at room temperature for 3 h, the reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography [hexane/AcOEt (2:1)] to give **5d** (97 mg, 57% yield) as colorless oil. IR (neat) ν cm^{-1}; 3608, 3448, 3048, 2896. ^{1}H NMR (400 MHz, $CDCl_3$) δ; 2.59 (1H, brs), 3.95–4.10 (2H, br), 4.10–4.20 (1H, br), 4.85 (1H, t, J=9.2 Hz), 5.36–5.49 (1H, m), 5.86–5.95 (1H, m), 7.33–7.40 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 58.6 (d, J=3.2 Hz), 75.5 (t, J=30.3 Hz), 120.7 (t, J=245.4 Hz), 122.0 (t, J=26.5 Hz), 127.7, 128.1, 128.7, 136.0 (d, J=3.6 Hz), 138.3 (t, J=5.1 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −37.7 (1F, ddd, J=253, 12, 12 Hz), −38.9 (1F, ddd, J=253, 12, 12 Hz). EI-MS m/z; 196 (M^+-H_2O), 107, 90, 77. HRMS; calcd for $C_{11}H_{10}F_2O$ (M^+-H_2O): 196.0700. Found: 196.0716.

4.2.5. (*Z*)-4,4-Difluoro-6-phenyl-2-hexene-1,5-diol (5e). After a mixture of ethyl (*Z*)-2,2-difluoro-4-phenyl-3-(tetrahydro-2*H*-pyran-2-yloxy)-butanoate (1.90 g, 5.98 mmol) and Red-Al™ (65% toluene solution, 4.3 ml, 7.18 mmol) in THF (15 ml) was stirred at −78 °C for 30 min, the reaction mixture was quenched with 5% HCl. Extractive workup (AcOEt for extraction) followed by concentration in vacuo left an oily aldehyde, which was used for the next step without further purification. Under an argon atmosphere, to a mixture of NaH (60% in oil, 264 mg, 6.58 mmol) and triethyl phosphonoacetate (1.92 g, 5.98 mmol) in DMF (10 ml) at 0 °C was added the aldehyde mentioned above in DMF (5 ml), and the mixture was stirred for 20 min. The reaction mixture was quenched with 5% HCl, extracted with ether. The combined organic layer was washed with $NaHCO_3$aq, brine and dried over anhydrous Na_2SO_4 and then evaporated in vacuo. The residue was purified by silica gel column chromatography [hexane/AcOEt (20:1)] to give a diastereomeric mixture of ethyl (*Z*)-4,4-difluoro-6-phenyl-5-(tetrahydro-2*H*-pyran-2-yloxy)-2-hexenoate (1.25 g, 59% yield), which was separated by MPLC [hexane/AcOEt (5:1)] to give less polar isomer and more polar isomer in the order of elution. Less polar: colorless oil. IR (neat) ν cm^{-1}; 1732. ^{1}H NMR (400 MHz, $CDCl_3$) δ; 1.29 (3H, t, J=7.2 Hz), 1.21–1.33 (1H, m), 1.36–1.49 (1H, m), 1.56–1.73 (3H, m), 2.77–2.85 (1H, m), 2.86 (1H, dd, J=14.2, 9.1 Hz), 2.98–3.05 (1H, m), 3.04 (1H, dd, J=14.2, 4.2 Hz), 4.23 (2H, q, J=7.2 Hz), 4.49–4.59 (1H, m), 4.95 (1H, t, J=2.7 Hz), 5.97 (1H, dt, J=14.6, 12.7 Hz), 6.09 (1H, dt, J=12.7, 1.6 Hz), 7.17–7.23 (1H, m), 7.25–7.32 (4H, m). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −38.7 (1F, ddd, J=257, 13, 13 Hz), −40.9 (1F, ddd, J=257, 14, 8 Hz). EI-MS m/z; 355 (M^++H), 252. Anal. Calcd for $C_{19}H_{24}F_2O_4$: C, 64.39; H, 6.83. Found: C, 64.53; H, 6.83. more polar: colorless oil. IR (neat) ν cm^{-1}; 1744. ^{1}H NMR (400 MHz, $CDCl_3$) δ; 1.30 (3H, t, J=7.2 Hz), 1.25–1.47 (5H, m), 1.63–1.74 (1H, m), 2.83 (1H, dd, J=14.0, 9.8 Hz), 3.11 (1H, dd, J=14.0, 3.0 Hz), 3.32 (1H, dd, J=11.2, 4.9 Hz), 3.83 (1H, ddd, J=11.5, 5.9, 5.9 Hz), 3.96 (1H, t, J=3.5 Hz), 4.24 (2H, q, J=7.2 Hz), 4.38–4.48 (1H, m), 6.10–6.23 (2H, m), 7.20–7.31 (5H, m). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −37.2 (1F, ddd, J=258, 9, 9 Hz), −44.3 (1F, ddd, J=258, 13, 13 Hz). EI-MS m/z; 355 (M^++H), 271, 252. HRMS; calcd for $C_{19}H_{24}F_2O_4Na$ (M^++Na): 377.1540. Found: 377.1555. To a solution of the above obtained more polar isomer (1.25 g, 3.52 mmol) in THF (20 ml) was added dropwise DIBAL (0.95 M hexane solution, 15 ml, 14.0 mmol) at −78 °C, and then the mixture was quenched with water after being stirred for 30 min. The organic layer was decanted and the residue was washed with ether twice. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography [hexane/AcOEt (3:1)] to give (*Z*)-4,4-difluoro-6-phenyl-5-(tetrahydro-2*H*-pyran-2-yloxy)-hexenol (**THP-5e**). After a mixture of **THP-5e** and a catalytic amount of *p*-toluenesulfonic acid in MeOH (10 ml) was stirred at room temperature for 1 h, the reaction mixture was concentrated in vacuo and the residue was purified by silica gel column chromatography [hexane/AcOEt (2:1)] to give **5e** (465 mg, 58% yield) as colorless oil. IR ($CHCl_3$) ν cm^{-1}; 3608, 3440, 3024, 2932, 1954, 1660, 1602. ^{1}H NMR (400 MHz, $CDCl_3$) δ; 2.66 (1H, dd, J=14.0, 10.6 Hz), 2.74 (1H, brs), 3.00 (1H, dd, J=14.0, 1.5 Hz), 3.16 (1H, d, J=2.6 Hz), 3.87–4.00 (1H, m), 4.31 (2H, s), 5.58 (1H, dd, J=15.6, 28.3 Hz), 5.95–6.07 (1H, m), 7.22–7.33 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 36.4, 58.8, 74.5 (t, J=30.2 Hz), 121.0 (t, J=244.6 Hz), 122.3 (t, J=26.6 Hz), 126.8, 128.6, 129.3, 137.2, 138.5 (t, J=5.2 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −37.7 (1F, dd, J=256, 2 Hz), −43.0 (1F, dt, J=256, 14 Hz). EI-MS m/z; 229 (M^++H), 210. HRMS; calcd for $C_{12}H_{15}F_2O_2$ (M^++H): 229.1040. Found: 229.1070.

4.3. Preparation of (*E*)-4,4-difluoro-5-phenyl-2-pentenol derivatives

4.3.1. 4,4-Difluoro-5-phenyl-2-pentenol (9c). After a mixture of ethyl 2,2-difluoro-3-phenylpropionate[37] (1.29 g, 7.6 mmol) in THF (10 ml) and DIBAL (11.4 ml, 1 M

hexane solution, 11.4 mmol) was stirred at −78 °C for 30 min, the reaction mixture was quenched by water followed by the similar extractive workup procedure used for **THP-5e** gave an oily aldehyde, which was used for the next step without further purification. To a suspension of NaH (60% oil, 334 mg, 8.36 mmol) in THF (10 ml) was added triethyl phosphonoacetate (1.874 g, 8.36 mmol) in THF (10 ml) at 0 °C, and after 10 min, to this mixture was added the solution of previous aldehyde in THF (10 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h and the reaction mixture was quenched with 5% HCl, extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography [hexane/AcOEt (20:1)] to give a crude mixture, which was further separated by MPLC [hexane/AcOEt (30:1)] to give ethyl (*E*)-4,4-difluoro-5-phenylpent-2-enoate (310 mg, 17% yield) and starting material (240 mg, 15% yield) in the order of elution. Ethyl (*E*)-4,4-difluoro-5-phenylpent-2-enoate: colorless oil. IR (neat) ν cm^{-1}; 3035, 2984, 2929, 1727. ^1H NMR (400 MHz, $CDCl_3$) δ; 1.29 (3H, t, J=7.2 Hz), 3.25 (2H, t, J=16.0 Hz), 4.21 (2H, q, J=7.2 Hz), 6.18 (1H, dt, J=15.6, 11.6 Hz), 6,76 (1H, dt, J=15.6, 2.4 Hz), 7.22–7.38 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ;.13.79, 43.45 (t, J=26.1 Hz), 60.79, 119.15 (t, J=241.4 Hz), 124.97 (t, J=8.5 Hz), 127.34, 128.20, 130.17, 131.37, 138.60 (t, J=27.3 Hz), 164.67. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −34.61 (2F, m). A mixture of the above ester (51 mg, 0.21 mmol) in THF (5 ml) and DIBAL (1 M hexane solution, 0.84 mmol) was stirred at −78 °C for 1 h. Usual extractive workup mentioned above and purification by silica gel column chromatography [hexane/AcOEt (2:1)] gave **9c** (42 mg, quantitative) as colorless oil. IR (neat) ν cm^{-1}; 3624, 3300–3600, 2932, 1682, 1604. ^1H NMR (400 MHz, $CDCl_3$) δ;1.77–1.93 (1H, brs), 3.20 (2H, t, J=15.7 Hz), 4.08–4.16 (2H, brs), 5.71–5.83 (1H, m), 6.05–6.14 (1H, m), 7.18–7.35 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 44.1 (t, J=27.6 Hz), 61.6, 120.3 (t, J=240.2 Hz), 124.4 (t, J=26,6 Hz), 127.3, 128.3, 130.5, 132.8 (t, J=4.2 Hz), 134.6 (t, J=8.3 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −31.77 (2F, td, J=22.5, 15 Hz).

4.3.2. 4,4-Difluoro-5-(4-methoxyphenylamino)-5-phenyl-2-penten-1-ol (13a). Compound **13a** was prepared from 3,3-difluoro-1-(4-methoxyphenyl)-4-phenylazetidin-2-one[38] through the reduction by DIBAL followed by Horner–Emmons reaction. Colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ; 1.40–1.65 (2H, br), 3.69 (3H, s), 4.17–4.27 (2H, m), 4.62 (1H, t, J=11.0 Hz), 5.80–5.96 (1H, m), 6.16–6.20 (1H, m), 6.50–6.56 (2H, m), 6.64–6.72 (2H, m), 7.24–7.45 (5H, m). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −40.4 (1F, d, J=244 Hz), −42.0 (1F, dt, J=244 Hz). EI-MS *m/z*; 319 (M^+), 212 (M^+−Anis).

4.4. General procedure for the reaction of difluoroallylic alcohol derivatives 5 with lithium dimethylcuprate in the presence of Me_3Al

4.4.1. (1*R,2*Z*,4*S**)-2-Fluoro-4-methyl-1-phenyl-2-pentene-1,5-diol (*syn*-6a-1).** To a mixture of **5a** (107 mg, 0.5 mmol) and Me_3Al (1 M hexane solution, 5 ml, 5 mmol) in THF (3 ml), was added at −30 °C the Gilman reagent prepared from CuI (476 mg, 2.5 mmol) and MeLi (1.14 M diethyl ether solution, 4.4 ml, 5 mmol) in THF (3 ml). After being stirred at 0 °C for 1.5 h, the reaction mixture was quenched with 5% HCl and filtered through celite pad. The filtrate was extracted with AcOEt and washed with $NaHCO_3$aq and brine. The organic layer was dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography [hexane/AcOEt (1:1)] to give *syn*-**6a-1** (92 mg, 88% yield) as colorless crystals. Mp 102–104 °C. IR ($CHCl_3$) ν cm^{-1}; 3616, 3150–3555, 2968, 2878, 1707. ^1H NMR (400 MHz, $CDCl_3$) δ; 1.01 (3H, d, J=6.9 Hz), 1.68–1.90 (1H, brs), 2.79–2.90 (1H, m), 3.41 (1H, dd, J=10.5, 7.8 Hz), 3.55 (1H, dd, J=10.5, 5.6 Hz), 4.82 (1H, dd, J=37.4, 9.6 Hz), 5.20 (1H, d, J=10.7 Hz), 7.28–7.44 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 16.8, 32.0 (d, J=2.6 Hz), 67.4, 72.5 (d, J=33.1 Hz), 109.5 (d, J=12.6 Hz), 126.7, 128.5 (d, J=22.5 Hz), 139.5, 158.6, 161.1. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −56.5 (1F, dd, J=37.4, 10.5 Hz). EI-MS *m/z*; 190 (M^+−HF), 162, 147. Anal. Calcd for $C_{12}H_{15}F_2O_2$: C, 68.55; H, 7.19. Found: C, 68.51; H, 7.19.

4.4.2. (2*R,3*Z*,5*R**)-4-Fluoro-2-methyl-6-phenyl-3-hexene-1,5-diol (*anti*-6c-1) and (*E*)-4-fluoro-2-methyl-6-phenyl-3-hexene-1,5-diol (*E*-6c-1).** Compound *anti*-**6c-1** was prepared from **5e** and Gilman reagent. Purification by silica gel column chromatography [hexane/AcOEt (1:1)] gave a mixture of **6c-1** (100 mg, 89% yield, *Z*/*E*=14:1, *syn*/*anti*=1:2 for *Z*-isomer), which was further purified by MPLC [hexane/AcOEt (1:1)] to give *E*-**6c-1**, *syn*-**6c-1**, *anti*-**6c-1** in the order of elution. *anti*-**6c-1**: colorless oil. IR (neat) ν cm^{-1}; 3682, 3604, 3414, 3013, 2962, 2875, 2400, 1708. ^1H NMR (400 MHz, $CDCl_3$) δ; 0.87 (3H, d, J=6.9 Hz), 2.30 (1H, brs), 2.71–2.84 (1H, m), 2.92 (1H, dd, J=13.6, 7.2 Hz), 3.00 (1H, dd, J=13.6, 6.3 Hz), 3.15 (1H, brs), 3.27 (1H, dd, J=10.5, 8.2 Hz), 3.49 (1H, dd, J=10.6, 5.2 Hz), 4.27 (1H, dt, J=17.4, 6.7 Hz), 4.51 (1H, dd, J=37.5, 9.6 Hz), 7.20–7.32 (5H,m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 16.6, 31.8 (d, J=1.7 Hz), 40.1, 67.3, 71.8 (d, J=30.0 Hz), 110.1 (d, J=12.9 Hz), 126.7, 128.4, 129.5, 137.1, 159.2 (d, J=258.6 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −62.4 (1F, dd, J=35, 18 Hz). EI-MS *m/z*: 224 (M^+), 207, 204. HRMS; calcd for $C_{13}H_{17}FO_2$ (M^+); 224.1213. Found: 224.1208. *E*-**6c-1**: colorless oil. IR (neat) ν cm^{-1}; 3687, 3599, 3424, 3028, 2965, 2930, 2875, 2401, 1697. ^1H NMR (400 MHz, $CDCl_3$) δ; 0.90 (3H, dd, J=6.7, 0.6 Hz), 2.31–2.48 (2H, m), 2.97 (1H, dd, J=10.3, 8.6 Hz), 3.00 (1H, dd, J=13.3, 6.8 Hz), 3.04 (1H, dd, J=13.3, 7.2 Hz), 3.23 (1H, dd, J=10.3, 4.8 Hz), 4.61 (1H, dt, J=22.7, 7.0 Hz), 4.90 (1H, dd, J=22.5, 10.7 Hz), 7.23–7.34 (5H, m). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −57.0 (1F, dd, J=23, 23 Hz). EI-MS *m/z*; 225 (M^++H), 207 (M^+−OH), 187. HRMS; calcd for $C_{13}H_{16}FO$ (M^+−OH): 207.1185. Found: 207.1183.

4.5. General procedure for the reaction of difluoroallylic alcohol derivatives 5 with trialkylaluminum in the presence of CuI·2LiCl

4.5.1. (2*R,3*Z*,5*S**)-4-Fluoro-2-methyl-7-phenyl-3-heptene-1,5-diol (*syn*-6b-1).** To a solution of **5b** (121 mg, 0.5 mmol) in THF (3 ml) was added Me_3Al (1 M hexane solution, 2.5 ml, 2.5 mmol) at −30 °C, and then copper

reagent prepared from CuI (468 mg, 2.5 mmol) and LiCl (212 mg, 5 mmol) in THF (3 ml) was added at −30 °C.[21] After being stirred at 0 °C for 20 h, the reaction mixture was quenched with 5% HCl and filtered through celite pad. The filtrate was extracted with AcOEt and washed with $NaHCO_3$aq and brine. The organic layer was dried over anhydrous Na_2SO_4, and then concentrated in vacuo. Purification by silica gel column chromatography [hexane/AcOEt (1:1)] gave a mixture (115 mg) of *syn*-**6b-1** (65% yield) and **5b** (31% recovery), which was further purified by MPLC [hexane/AcOEt (1:1)] to give **5b** and *syn*-**6b-1** in the order of elution. *syn*-**6b-1**: colorless oil. IR ($CHCl_3$) ν cm^{-1}; 3620, 3432, 3032, 2964, 2936, 2876, 1706, 1602. ^1H NMR (400 MHz, $CDCl_3$) δ; 0.99 (3H, d, $J=6.8$ Hz), 1.88–2.06 (2H, m), 2.65–2.87 (3H, m), 3.37 (1H, dd, $J=10.5$, 7.9 Hz), 3.55 (1H, dd, $J=10.5$, 5.4 Hz), 4.09 (1H, ddd, $J=12.8$, 7.6, 5.1 Hz), 4.72 (1H, dd, $J=38.3$, 9.5 Hz), 7.16–7.34 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 16.8, 31.5, 31.8 (d, $J=2.7$ Hz), 35.6, 67.4, 69.4 (d, $J=31.6$ Hz), 108.4 (d, $J=12.8$ Hz), 125.9, 128.4, 128.4, 141.4, 160.9 (d, $J=257.8$ Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −60.3 (1F, dd, $J=38$, 15 Hz). EI-MS *m/z*; 238(M^+), 220(M^+-H_2O), 201, 190, 91. HRMS; calcd for $C_{14}H^{19}FO_2$ (M^+): 238.1369. Found: 238.1370.

4.5.2. (1*R,2*Z*,4*S**)-2-Fluoro-4-isobutyl-1-phenyl-2-pentene-1,5-diol (*syn*-6a-2).** Compound *syn*-**6a-2** was prepared from **5a** and triisobutylaluminum. Purification by silica gel column chromatography [hexane/AcOEt (1:1)] afforded a mixture (124 mg) of *syn*-**6a-2** (68% yield) and **5a** (30% recovery), which was further purified by MPLC [hexane/AcOEt (1:1)] to give **5a** and *syn*-**6a-2** in the order of elution. *syn*-**6a-2**: colorless crystals. Mp 67–68 °C. IR ($CHCl_3$) ν cm^{-1}; 3616, 3150–3570, 2956, 1706, 1452. ^1H NMR (400 MHz, $CDCl_3$) δ; 0.85 (3H, d, $J=6.7$ Hz), 0.88 (3H, d, $J=6.7$ Hz), 1.13 (2H, dd, $J=7.3$ Hz), 1.54 (1H, qqt, $J=6.7$, 6.7, 6.7 Hz), 2.77–2.89 (1H, m), 3.31 (1H, dd, $J=10.6$, 8.5 Hz), 3.55 (1H, dd, $J=10.6$, 4.7 Hz), 4.68 (1H, dd, $J=37.4$, 10.1 Hz), 5.17 (1H, d, $J=8.6$ Hz), 7.28–7.44 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 21.8, 23.4, 25.7, 35.4, 40.3, 66.4, 72.3 (d, $J=34.4$ Hz), 108.4 (d, $J=12.4$ Hz), 126.8, 128.2, 128.5, 139.7, 161.2 (d, $J=256.7$ Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −54.4 (1F, d, $J=37$ Hz). EI-MS *m/z*; 204 ($M^+ + H - H_2O - CH_2OH$). HRMS; calcd for $C_{14}H_{17}F$ ($M^+ + H - H_2O - CH_2OH$): 204.1314. Found: 204.1313.

4.5.3. (2*R,3*Z*,5*S**)-4-Fluoro-2-isobutyl-7-phenyl-3-heptene-1,5-diol (*syn*-6b-2).** Compound *syn*-**6b-2** was prepared from **5b** and triisobutylaluminum. Purification by silica gel column chromatography [hexane/AcOEt (1:1)] gave a mixture (127 mg) of *syn*-**6b-2** (66% yield) and **5b** (29% recovery) which was further purified by MPLC [hexane/AcOEt (1:1)] to give *syn*-**6b-2** and **5b** in the order of elution. *syn*-**6b-2**: colorless oil. IR ($CHCl_3$) ν cm^{-1}; 3616, 3416, 3020, 2960, 1706, 1602, 1452. ^1H NMR (400 MHz, $CDCl_3$) δ; 0.89 (3H, d, $J=6.2$ Hz), 0.90 (3H, d, $J=6.3$ Hz), 1.17 (2H, dd, $J=7.3$, 7.3 Hz), 1.50–1.65 (1H, m), 1.87–2.05 (2H, m), 2.71–2.83 (3H, m), 3.36 (1H, dd, $J=10.5$, 8.2 Hz), 3.60 (1H, dd, $J=10.5$, 4.9 Hz), 4.12–4.14 (1H, m), 4.66 (1H, dd, $J=38.3$, 10.1 Hz), 7.18–7.31 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 21.7, 23.5, 25.7, 31.5, 35.4, 35.9, 40.4, 66.6, 69.4 (d, $J=32.5$ Hz), 107.2 (d, $J=12.9$ Hz), 125.9, 128.4, 128.5, 141.5, 161.9 (d, $J=257.2$ Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −56.8 (1F, dd, $J=38$, 13 Hz). EI-MS *m/z*; 280 (M^+), 243, 232, 156, 91. HRMS; calcd for $C_{17}H_{25}FO_2$ (M^+): 280.1839. Found: 280.1821.

4.5.4. (2*R,3*Z*,5*S**)-4-Fluoro-2-methyl-6-phenyl-3-hexene-1,5-diol (*syn*-6c-1).** Compound *syn*-**6c-1** was prepared from **5c** and trimethylaluminum. Purification by silica gel column chromatography [hexane/AcOEt (1:1)] gave *syn*-**6c-1** (110 mg, 98% yield) as colorless oil. IR ($CHCl_3$) ν cm^{-1}; 3608, 3416, 3024, 2872, 1706. ^1H NMR (400 MHz, $CDCl_3$) δ; 0.93 (3H, d, $J=6.9$ Hz), 2.70–2.83 (1H, m), 2.88 (1H, dd, $J=13.6$, 7.5 Hz), 2.99 (1H, dd, $J=13.6$, 6.0 Hz), 3.24 (1H, dd, $J=10.6$, 7.8 Hz), 3.42 (1H, dd, $J=10.6$, 5.4 Hz), 4.26 (1H, ddd, $J=13.6$, 7.5, 6.0 Hz), 4.56 (1H, dd, $J=38.2$, 9.6 Hz), 7.20–7.32 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 16.6, 31.7 (d, $J=2.7$ Hz), 40.5, 67.1, 71.3 (d, $J=31.9$ Hz), 109.0 (d, $J=12.5$ Hz), 126.6, 128.3, 129.4, 137.1, 159.7 (d, $J=257.9$ Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −61.0 (1F, dd, $J=38.2$, 13.6 Hz). EI-MS *m/z*; 224 (M^+), 204, 187, 176, 91. HRMS; calcd for $C_{13}H_{17}FO_2$ (M^+): 224.1213. Found: 224.1213.

4.5.5. (2*R,3*Z*,5*S**)-4-Fluoro-2-isobutyl-6-phenyl-3-hexene-1,5-diol (*syn*-6c-2).** Compound *syn*-**6c-2** was prepared from **5c** and triisobutylaluminum. Purification by silica gel column chromatography [hexane/AcOEt (1:1)] gave a mixture (125 mg) of *syn*-**6c-2** (78% yield) and **5c** (19% recovery), which was further purified by MPLC [hexane/AcOEt (1:1)] to give **5c** and *syn*-**6c-2** in the order of elution. *syn*-**6c-2**: colorless solid. Mp 70–72 °C. IR ($CHCl_3$) ν cm^{-1}; 3610, 3412, 2932, 2872, 1707. ^1H NMR (400 MHz, $CDCl_3$) δ; 0.86 (3H, d, $J=6,4$ Hz), 0.86 (3H, d, $J=6,7$ Hz), 1,04–1.16 (2H, m), 1.39–1.54 (1H, m), 1.65 (1H, br), 2.59 (1H, br), 2.71–2.83 (1H, m), 2.92 (1H, dd, $J=13.6$, 7.1 Hz), 3.01 (1H, dd, $J=13.6$, 6.2 Hz), 3.24 (1H, dd, $J=10.6$, 8.0 Hz), 3.47 (1H, dd, $J=10.6$, 4.9 Hz), 4.26–4.37 (1H, m), 4.48 (1H, dd, $J=38.0$, 10.1 Hz), 7.20–7.33 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 21.7, 23.5, 25.5, 35.5 (d, $J=1.5$ Hz), 40.4, 40.6, 66.5, 71.5(d, $J=32.1$ Hz), 108.2 (d, $J=12.5$ Hz), 126.8, 128.5, 129.5, 137.0, 160.4 (d, $J=257.4$ Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −59.3 (1F, dd, $J=37.7$, 10.5 Hz). EI-MS *m/z*; 267 ($M^+ + H$), 246 ($M^+ - HF$), 218, 91. HRMS; calcd for $C_{16}H_{23}FO_2$ (M^+): 266.1682. Found: 266.1692.

4.5.6. (1*R,2*Z*,4*R**)-2-Fluoro-4-methyl-1-phenyl-2-pentene-1,5-diol (*anti*-6a-1).** Compound *anti*-**6a-1** was prepared from **5d** and trimethylaluminum. Purification by silica gel column chromatography [hexane/AcOEt (1:1)] gave a mixture (104 mg) of *syn*- and *anti*-**6a-1** (52% yield, *syn*/*anti*=1:10.5) and **5d** (41% recovery). This mixture was purified by MPLC [hexane/AcOEt (2:3)] to give **5d**, *syn*-**6a-1** and *anti*-**6a-1** in the order of elution. *anti*-**6a-1**: colorless crystals. Mp 56–58 °C. IR ($CHCl_3$) ν cm^{-1}; 3608, 3396, 3040, 3016, 2968, 2872, 1700. ^1H NMR (400 MHz, $CDCl_3$) δ; 0.96 (3H, d, $J=6.8$ Hz), 2.67–2.88 (1H, m), 3.34 (1H, dd, $J=10.5$, 8.2 Hz), 3.53 (1H, dd, $J=10.5$, 5.3 Hz), 3.95 (1H, brs), 4.80 (1H, dd, $J=36.7$, 9.6 Hz), 5.17 (1H, d, $J=16.7$ Hz), 7.26–7.46 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 16.6, 31.9 (d, $J=2.2$ Hz), 67.3, 72.8 (d, $J=30.4$ Hz), 110.5 (d, $J=12.9$ Hz), 126.6, 128.1, 128.4, 139.3, 159.4 (d, $J=258.9$ Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −60.1 (1F, dd, $J=37$, 17 Hz). EI-MS *m/z*; 190 ($M^+ - HF$),

162, 150, 147. HRMS; calcd for $C_{12}H_{14}FO_2$ (M^+-HF): 190.0994. Found: 190.1008.

4.5.7. (1*R,2*Z*,4*R**)-2-Fluoro-4-isobutyl-1-phenyl-2-pentene-1,5-diol (*anti*-6a-2).** Compound *anti*-**6a**-**2** was prepared from **5d** and triisobutylaluminum. Purification by silica gel column chromatography [hexane/AcOEt (1:2)] gave a mixture (94 mg) of *syn*- and *anti*-**6a**-**2** (23% yield, *syn*/*anti*=1:5.8) and **5d** (60% recovery), which was further purified by MPLC [hexane/AcOEt (2:3)] to give **5d**, *syn*-**6a**-**2** and *anti*-**6a**-**2** in the order of elution. *anti*-**6a**-**2**: colorless oil. IR ($CHCl_3$) ν cm^{-1}; 3612, 3416, 3024, 2960, 2872, 1700, 1600, 1368. ^1H NMR (400 MHz, $CDCl_3$) δ; 0.85 (3H, d, J=6,6 Hz), 0.89 (3H, d, J=6,6 Hz), 1,13–1.21 (2H, m), 1.49–1.64 (1H, m), 1.85 (1H, brs), 2.76–2.88 (1H, m), 3.30 (1H, brs), 3.39 (1H, dd, J=10.5, 8.1 Hz), 3.60 (1H, dd, J=10.5, 5.0 Hz), 4.76 (1H, dd, J=36.7, 10.1 Hz), 5.22 (1H, d, J=15.5 Hz), 7.26–7.44 (5H, m).^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 21.8, 23.5, 25.7, 35.6, 40.4, 66.5, 72.8 (d, J=31.1 Hz), 109.5 (d, J=12.9 Hz), 126.5, 128.2, 128.5, 139.4, 160.3 (d, J=258.0 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −59.6 (1F, d, J=35 Hz). EI-MS *m*/*z*; 232 (M^+-HF), 204, 150, 117, 91. HRMS; calcd for $C_{14}H_{17}F$ ($M^+-OH-CH_2OH$): 204.1314. Found: 204.1311.

4.5.8. (2*R,3*Z*,5*R**)-4-Fluoro-2-isobutyl-6-phenyl-3-hexene-1,5-diol (*anti*-6c-2).** Compound *anti*-**6c**-**2** was prepared from **5e** and triisobutylaluminum. Purification by silica gel column chromatography [hexane/AcOEt (1:1)] gave a mixture (123 mg) of *syn*- and *anti*-**6c**-**2** (32% yield, *syn*/*anti*=1:2.9) and **5e** (32% recovery), which was further purified by MPLC [hexane/AcOEt (1:1)] to give **5e**, *syn*-**6c**-**2** and *anti*-**6c**-**2** in the order of elution. *anti*-**6c**-**2**: colorless solid. Mp 48–49 °C. IR (neat) ν cm^{-1}; 3677, 3602, 3401, 2957, 2871, 1707. ^1H NMR (400 MHz, $CDCl_3$) δ; 0.77 (3H, d, J=6.6 Hz), 0.79 (3H, d, J=6.5 Hz), 0.90–1.06 (2H, m), 1.08–1.22 (1H, m), 2.40 (1H, br), 2.69–2.81 (1H, m), 2.97 (1H, dd, J=13.8, 6.6 Hz), 3.00 (1H, dd, J=13.8, 7.6 Hz), 3.24 (1H, dd, J=10.5, 8.8 Hz), 3.44 (1H, br), 3.53 (1H, dd, J=10.5, 4.7 Hz), 4.31 (1H, dt, J=19.8, 7.0 Hz), 4.38 (1H, dd, J=37.0, 10.2 Hz), 7.19–7.30 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 21.5, 23.6, 25.2, 35.6, 39.8, 40.1, 66.6, 72.3 (d, J=29.5 Hz), 109.9 (d, J=13.3 Hz), 126.6, 128.4, 129.4, 136.9, 159.9 (d, J=258.8 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −64.2 (1F, dd, J=37, 19 Hz). EI-MS *m*/*z*; 289 (M^++Na), 229. HRMS; calcd for $C_{16}H_{23}FO_2Na$ (M^++Na); 289.1580. Found: 289.1575.

4.5.9. (*Z*)-5-[(*tert*-Butyldiphenylsilanyl)oxy]-2-fluoro-4-methyl-1-phenyl-2-penten-1-ol (10a). Compound **10a** was prepared from **9a** and Me_3Al in the presence CuI·2LiCl. Purification by silica gel column chromatography [hexane/AcOEt (20:1)] afforded a mixture of *syn*-**10a** (77% yield), *anti*-**10a** (4% yield) and **9a** (4% recovery). **10a** was desilylated with TBAF and the product was identical with **6a**-**1**.

4.5.10. (*E*)-5-[(*tert*-Butyldiphenylsilanyl)oxy]-2,2-difluoro-1-phenyl-3-penten-1-ol (9a). A mixture of **5a** (321 mg, 1.5 mmol), imidazole (112 mg, 1.65 mmol) and *tert*-butyldiphenylchlorosilane (454 mg, 1.65 mmol) in DMF (6 ml) was stirred at room temperature for 3 h. Extractive workup (AcOEt for extraction) followed by silica gel column chromatography [hexane/AcOEt (10:1)] gave **9a** (680 mg, quantitative) as colorless oil. IR ($CHCl_3$) ν cm^{-1}; 3680, 3616, 3028, 1602. ^1H NMR (400 MHz, $CDCl_3$) δ; 1.05 (9H, s), 2.53 (1H, d, J=3.8 Hz), 4.24 (2H,m), 4.93 (1H, td, J=9.4, 3.8 Hz), 5.90–6.03 (1H, m), 6.08–6.16 (1H, m), 7.30–7.50 (11H, m), 7.59–7.68 (4H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 19.2, 26.7, 62.6, 76.1 (t, J=30.0 Hz), 120.2 (t, J=25.0 Hz), 120.2 (t, J=244.1 Hz), 127.6, 127.8, 128.2, 128.6, 129.8, 133.1, 135.4, 136.2, 136.6 (t, J=8.1 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −43.3 (1F, d, J=9.4 Hz), −43.5 (1F, d, J=9.4 Hz). EI-MS *m*/*z*; 375 (M^+-Ph), 305, 247. Anal. Calcd for $C_{27}H_{30}F_2O_2Si$: C, 71.65; H, 6.68. Found: C, 71.49; H, 6.70.

4.6. Preparation of the pivalate

4.6.1. (2*S,3*Z*,5*R**)-4-Fluoro-5-hydroxy-2-methyl-7-phenyl-hept-3-enyl-2,2-dimethyl-propionate (7b-1).** After a mixture of *syn*-**6b**-**1** (210 mg, 0.88 mmol), pivaloyl chloride (121 mg, 1.0 mmol) and pyridine (0.20 ml) in CH_2Cl_2 (7 ml) was stirred at room temperature for 4.5 h, usual extractive workup followed by the purification by silica gel column chromatography [hexane/AcOEt (5:1)] gave **7b**-**1** (218 mg, 77% yield) as colorless oil. IR (neat) ν cm^{-1}; 3450, 2970, 1728, 1710. ^1H NMR (400 MHz, $CDCl_3$) δ; 1.05 (3H, t, J=6.9 Hz), 1.20 (9H, s), 1.90–2.05 (2H, m), 2.12–2.28 (1H, brs), 2.66–2.81 (2H, m), 2.94–3.06 (1H, m), 3.92 (1H, dd, J=10.7, 6.6 Hz), 3.96 (1H, dd, J=10.7, 6.1 Hz), 4.02–4.12 (1H, m), 4.71 (1H, dd, J=37.3, 9.5 Hz), 7.17–7.22 (3H, m), 7.25–7.32 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 17.2, 27.1. 28.7 (d, J=3.7 Hz), 31.4, 35.4, 38.8, 68.0, 69.7 (d, J=30.3 Hz), 108.3 (d, J=13.2 Hz), 126.0, 128.4, 141.2, 159.9 (d, J=259.1 Hz), 178.5. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −60.7 (1F, dd, J=37.0, 2.0 Hz). EI-MS *m*/*z*; 304 (M^+-H_2O), 220. 202. Anal. Calcd for $C_{19}H_{27}FO_3$: C, 70.78; H, 8.44. Found: C, 70.43; H, 8.37.

4.6.2. (2*S,3*Z*,5*R**)-4-Fluoro-5-hydroxy-2-methyl-6-phenyl-hex-3-enyl-2,2-dimethyl-propionate (7c-1).** Compound **7c**-**1** was prepared from *syn*-**6c**-**1**. Purification by silica gel column chromatography [hexane/AcOEt (5:1)] afforded **7c**-**1** (80% yield) as colorless oil. IR (neat) ν cm^{-1}; 3456, 2972, 2929, 2876, 1730, 1712. ^1H- NMR (400 MHz, $CDCl_3$) δ; 1.01 (3H, d, J=6.9 Hz), 1.19 (9H, s), 2.02 (1H, d, J=4.9 Hz), 2.85–3.04 (3H, m), 3.82–3.91 (2H, m), 4.26–4.32 (1H, m), 4.64 (1H, dd, J=37.5, 9.5 Hz), 7.19–7.35 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 17.1, 27.1, 28.7 (d, J=3.8 Hz), 38.8, 40.7, 67.9, 71.2 (d, J=31.4 Hz), 108.3 (d, J=12.6 Hz), 126.8, 128.5, 129.5, 136.8, 159.2 (d, J=258.2 Hz), 178.4. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −60.0 (1F, dd, J=37, 13 Hz). EI-MS *m*/*z*; 331 (M^++Na), 291, 189. HRMS; calcd for $C_{18}H_{25}O_3FNa$ (M^++Na): 331.1685. Found: 331.1654. Anal. Calcd for $C_{18}H_{25}FO_3$: C, 70.10; H, 8.17. Found: C, 70.06; H, 8.14.

4.7. Preparation of the *N*-Boc derivative 8 through one-pot azidation reaction

4.7.1. (2*S,4*Z*,5*S**)-5-[(*tert*-Butoxycarbonyl)amino]-4-fluoro-2-methyl-7-phenyl-hept-3-en-1-ol (8b) and (2*S**,3*R**,4*Z*)-3-[(*tert*-butoxycarbonyl)amino]-4-fluoro-2-methyl-7-phenyl-hept-4-en-1-ol (17b).** To a mixture of

7b-**1** (260 mg, 0.81 mmol), DMAP (367 mg, 3 mmol) and NaN_3 (1.63 g, 25.0 mmol) in CH_2Cl_2 (10 ml) was added methanesulfonyl chloride (229 mg, 2.0 mmol) at 0 °C. After being stirred at room temperature for 30 min, to the reaction mixture was added DMSO (5 ml), and then the whole was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with a mixture of AcOEt and hexane. The aqueous layer was re-extracted with AcOEt, and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by short silica gel column chromatography [hexane/AcOEt (5:1)] to give crude **15b** (266 mg, 95% yield). To a suspension of $LiAlH_4$ (76.0 mg, 2.0 mmol) in THF (3 ml) was added **15b** (266 mg) in THF (5 ml) at 0 °C, and then the whole was stirred at room temperature for 90 min. To the reaction mixture was added ice water dropwise at 0 °C and after being stirred for 10 min, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (2 ml) and to this solution were added Et_3N (0.28 ml, 0.28 mmol) and $(Boc)_2O$ (218 mg, 1.0 mmol) in CH_2Cl_2 (2 ml). After being stirred at room temperature for 30 min, the reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography [hexane/AcOEt (4:1)] to give a mixture of **8b** and **17b** (224 mg, 86% yield, **8b**:**17b**=8.4:1), which was further separated by MPLC [hexane/AcOEt (3:1)]. **8b**: colorless solid. Mp 82–84 °C. IR (neat) ν cm^{-1}; 3400, 3332, 2976, 2931, 1694. ^1H NMR (400 MHz, $CDCl_3$) δ; 0.10 (3H, d, J=6.8 Hz), 1.44 (9H, s), 1.80–2.02 (2H, m), 2.18 (1H, brs), 2.66 (2H, t, J=7.8 Hz), 2.76–2.89 (1H, m), 3.33–3.44 (1H, m), 3.44–3.55 (1H, m), 4.00–4.18 (1H, m), 4.61 (1H, dd, J=37.5, 9.7 Hz), 4.71–4.82 (1H, brd), 7.15–7.22 (3H, m), 7.25–7.31 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 16.7, 28.3, 32.1, 33.6, 52.2 (d, J=30.2 Hz), 67.2, 80.0, 110.4 (d, J=12.0 Hz), 126.1, 128.3, 128.5, 140.9, 155.2, 155.7 (d, J=260.0 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −62.8 (1F, dd, J=37.0, 22.0 Hz). EI-MS m/z; 360(M^++Na). Anal. Calcd for $C_{19}H_{28}FNO_3$: C, 67.63; H, 8.36; N, 4.15. Found: C, 67.66; H, 8.33; N, 4.13. **17b**: colorless oil. IR (neat) ν cm^{-1}; 3393, 2976, 2933, 1693, 1499. ^1H NMR (400 MHz, $CDCl_3$) δ; 0.94 (3H, d, J=7.0 Hz), 1.45 (9H, s), 1.71 (1H, br), 2.32–2.50 (2H, m), 2.68 (2H, t, J=7.6 Hz), 2.76 (1H, brs), 3.44 (1H, d, J=11.0 Hz), 3.66 (1H, d, J=10.2 Hz), 4.02 (1H, dt, J=24.3, 9.4 Hz), 4.81 (1H, dt, J=37.7, 7.5 Hz), 5.06 (1H, bd, d, J=9.0 Hz), 7.11–7.19 (3H, m), 7.19–7.29 (3H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 14.4, 25.1(d, J=4.0 Hz), 28.3, 35.3, 37.4, 54.4 (d, J=27.4 Hz), 63.7, 80.3, 107.4 (d, J=14.4 Hz), 126.0, 128.4 (d, J=9.1 Hz), 141.3, 156.3, 156.6 (d, J=256.1 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −62.0 (1F, dd, J=38, 24 Hz). EI-MS m/z; 338 (M^++H), 282, 264. HRMS; calcd for $C_{19}H_{29}FNO_3H$ (M^++H); 338.2131. Found: 338.2130.

4.7.2. *tert*-Butyl (1*R,2*Z*,4*R**)-1-benzyl-2-fluoro-5-hydroxy-4-methyl-2-pentenyl carbamate (8c).** Compound **8c** was prepared from **7c**-**1** (308 mg, 1.0 mmol). Purification by silica gel column chromatography [hexane/AcOEt (5:1)] afforded **8c** (235 mg) in 71% yield from **7c**-**1**. **8c**: colorless oil. IR (neat) ν cm^{-1}; 3427, 3334, 2976, 2931, 2872, 1697. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ; 0.92 (3H, d, J=6.9 Hz), 1.47 (9H, s), 1.67 (1H, brs), 2.77–2.83 (1H, m), 2.95–3.15 (2H, m), 3.37 (1H, dd, J=10.5, 7.3 Hz), 3.47 (1H, dd, J=10.5, 5.8 Hz), 4.35–4.46 (1H, m), 4.44 (1H, dd, J=37.9, 9.5 Hz), 4.74 (1H, brs), 7.19–7.36 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, 50 °C) δ; 16.5, 28.3, 32.2 (d, J=2.5 Hz), 38.6, 53.7 (d, J=29.2 Hz), 67.3, 80.0, 110.0 (d, J=12.9 Hz), 126.9, 128.4, 129.4, 136.8, 154.9, 157.4 (d, J=257.7 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −61.0 (1F, dd, J=38.0, 20.0 Hz). ES-MS m/z; 346 (M^++Na). HRMS Calcd for $C_{18}H_{26}FNO_3Na$: 346.1795 (M^++Na). Found: 346.1786.

References and notes

1. (a) Hann, M. M.; Sammes, P. G.; Kennewell, P. D.; Taylor, J. B. *J. Chem. Soc. Perkin Trans. 1* **1982**, 307–314. (b) Abraham, R. J.; Ellison, S. L. R.; Schonholzer, P.; Thomas, W. A. *Tetrahedron* **1986**, *42*, 2101–2110. (c) Cieplak, P.; Kollman, P. A. *J. Comput. Aided Mol. Des.* **1993**, *7*, 291–304. (d) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088–6089 and references cited therein. (e) Welch, J. T. In *Biomedical frontiers of fluorine chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; ACS: Washington, DC, 1996. (f) Howard, J. A. K.; Hoy, V. J.; O'Hagan, D.; Smith, G. T. *Tetrahedron* **1996**, *38*, 12613–12622. (g) O'Hagan, D.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1997**, 645–652.
2. (a) Alemendinger, T.; Furet, P.; Hungerbuehler, E. *Tetrahedron Lett.* **1990**, *31*, 7297–7300. (b) Alemendinger, T.; Felder, E.; Hungerbuehler, E. *Tetrahedron Lett.* **1990**, *31*, 7301–7304.
3. Boros, L. G.; De Corte, B.; Gimi, R. H.; Welch, J. T.; Wu, Y.; Handschumacher, R. E. *Tetrahedron Lett.* **1994**, *35*, 6033–6036.
4. (a) Welch, T.; Lin, J. *Tetrahedron* **1996**, *52*, 291–304. (b) Lin, J.; Toscano, P. J.; Welch, J. T. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 14020–14024. (c) Zhao, K.; Lim, D. S.; Funaki, T.; Welch, J. T. *Bioorg. Med. Chem.* **2003**, *11*, 207–215.
5. Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107–3111.
6. Examples of trifluoromethyl substituted peptide mimetics, [CH(CF_3)NH] as a replacement for [CONH] bond, see: (a) Volonterio, A.; Bravo, P.; Zanda, M. *Org. Lett.* **2000**, *2*, 1827–1830. (b) Molteni, M.; Volonterio, A.; Zanda, M. *Org. Lett.* **2003**, *5*, 3887–3890 and references cited therein.
7. Machleidt, H.; Wassendorf, R. *Ann.* **1964**, *674*, 1–10.
8. For a review of fluoroalkene syntheses using phosphonium ylides. Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641–1715.
9. Kinetic separation of 1-bromo-1-fluoroalkenes using palladium chemistry, see: (a) Xu, J.; Burton, D. J. *Org. Lett.* **2002**, *4*, 831–833. (b) Xu, J.; Burton, D. J. *Tetrahedron Lett.* **2002**, *43*, 4565–4567. See also: (c) Gross, R. S.; Mehdi, S.; McCarthy, J. R. *Tetrahedron Lett.* **1993**, *34*, 7197–7200.
10. Modification of Horner–Emmons type fluoroolefination reactions, see: (a) Sano, S.; Teranishi, R.; Nagao, Y. *Tetrahedron Lett.* **2002**, *43*, 9183–9186. (b) Sano, S.; Yokoyama, K.; Teranishi, R.; Shiro, M.; Nagao, Y. *Tetrahedron Lett.* **2002**, *43*, 281–284. (c) Sano, S.; Saito, K.; Nagao, Y. *Tetrahedron Lett.* **2003**, *44*, 3987–3990.
11. Highly *Z*-selective fluoroolefin synthesis via sulfoxide elimination reaction, see: (a) Allemendinger, T. *Tetrahedron*

1991, *47*, 4905–4914. (b) Nakazato, A.; Kumagai, T.; Sakagami, K.; Yoshikawa, R.; Suzuki, Y.; Chaki, S.; Ito, H.; Taguchi, T.; Nakanishi, S.; Okuyama, S. *J. Med. Chem.* **2000**, *43*, 4893–4909.

12. Hata, H.; Kobayashi, T.; Amii, H.; Uneyama, K.; Welch, J. T. *Tetrahedron Lett.* **2002**, *43*, 6099–6102.
13. 1-Arylsulfonyl-1-fluoroalkenes as a building block, see: (a) McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439–7440. (b) McCarthy, J. R.; Huber, E. W.; Le, T.-B.; Mark Laskovics, F.; Mattews, D. *Tetrahedron* **1996**, *52*, 45–58.
14. Ring-opening reaction of fluorinated cyclopropane derivatives, see: (a) Bessiere, Y.; Savary, D. N.-H.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 1739–1746. (b) Bessiere, Y.; Bessard, Y.; Kotani, T.; Schlosser, M. *Tetrahedron* **1991**, *47*, 4355–4360. (c) Taguchi, T.; Takigawa, T.; Tawara, Y.; Morikawa, T.; Kobayashi, Y. *Tetrahedron Lett.* **1984**, *25*, 5689–5692.
15. Cr(II)-mediated reaction of dibromofluoroacetate with aldehyde, see: Barma, D. K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falk, J. R. *J. Am Chem. Soc.* **2003**, *125*, 3218–3219.
16. (a) Otaka, A.; Watanabe, H.; Mitsuyama, E.; Yukimasa, A.; Tamamura, H.; Fujii, N. *Tetrahedron Lett.* **2001**, *42*, 285–287. (b) Otaka, A.; Watanabe, H.; Yukimasa, A.; Oishi, S.; Tamamura, H.; Fujii, N. *Tetrahedron Lett.* **2001**, *42*, 5443–5446. (c) Otaka, A.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Oishi, S.; Tamamura, H.; Fujii, N. *Chem. Commun.* **2003**, 1834–1835. (d) Otaka, A.; Mitsuyama, E.; Watanabe, H.; Tamamura, H.; Fujii, N. *Chem. Commun.* **2000**, 1081–1082.
17. 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.
18. Okada, M.; Nakamura, Y.; Sato, A.; Horikawa, H.; Saito, A.; Taguchi, T. *Chem. Lett.* **2002**, 28–29.
19. Okada, M.; Nakamura, Y.; Saito, A.; Sato, A.; Horikawa, H.; Taguchi, T. *Tetrahedron Lett.* **2002**, *43*, 5845–5848.
20. Yamazaki, A.; Shinohara, N.; Kitazume, T.; Sato, S. *J. Fluorine Chem.* **1997**, *97*, 91–96.
21. Lipshutz, B. H.; Segi, M. *Tetrahedron* **1995**, *51*, 4407–4420.
22. Copper-catalyzed conjugate additions of trialkylaluminium with enones, see: (a) Kabbara, J.; Fleming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Tetrahedron* **1995**, *51*, 743–754. (b) Takemoto, Y.; Kuraoka, S.; Hamaue, N.; Aoe, K.; Hiramatsu, H.; Iwata, C. *Tetrahedron* **1996**, *52*, 14177–14188. (c) Benett, S. M. W.; Brown, S. M.; Muxworthy, J. P.; Woodward, S. *Tetrahedron Lett.* **1999**, *40*, 1767–1770. (d) Pamies, O.; Net, G.; Ruiz, A.; Claver, C.; Woodward, S. *Tetrahedron: Asymmetry* **2000**, *11*, 871–877. (e) Kraus, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196.
23. Copper-catalyzed SN2′ substitution of allylic phosphates and chlorides with trialkylaluminum, see: Fleming, S.; Kabbara, J.; Nickish, K.; Westermann, J.; Mohr, J. *Synlett* **1995**, 183–185.
24. Maruoka demonstrated several specific reactions of fluorinated molecules based on fluorine–aluminum coordination. (a) Ooi, T.; Uraguchi, D.; Kagoshima, N.; Maruoka, K. *Tetrahedron Lett.* **1997**, *38*, 5679–5682. (b) Ooi, T.; Kagoshima, N.; Uraguchi, D.; Maruoka, K. *Tetrahedron Lett.* **1998**, *39*, 7105–7108. (c) Ooi, T.; Kagoshima, N.; Maruoka, K. *J. Am. Chem. Soc.* **1997**, *119*, 5754–5755. (d) Uraguchi, D.; Ooi, T.; Maruoka, K. *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 14–22. (e) Plenio, H. *Chem. Rev.* **1997**, *97*, 3363–3384.
25. Ito, H.; Saito, A.; Taguchi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1989–1994.
26. (a) Lipshuts, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135–631. (b) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750–3771.
27. *anti* mode reaction with allylic esters, halides and phosphates: (a) Goering, H. L.; Singleton, V. D. *J. Am. Chem. Soc.* **1976**, *98*, 7854–7855. (b) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 3986–3990. (c) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, *49*, 422–426. (d) Goering, H. L.; Kantner, S. S.; Seitz, E. P. *J. Org. Chem.* **1985**, *50*, 5495–5499. (e) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1981**, *46*, 2144–2148. (f) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884–2891. (g) Tseng, C. C.; Yen, S.-J.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2892–2895. (h) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063–3066. (i) Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, *111*, 3091–3093. (j) Ibuka, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420–7422.
28. *syn* mode reaction, in particular with allylic carbamate derivatives, see: (a) Gallina, C.; Clattini, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035–1036. (b) Goering, H. L.; Kantner, S. S.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 715–721. (c) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1985**, *50*, 1597–1599. (d) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N. *J. Org. Chem.* **1991**, *56*, 4370–4382. (e) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **2000**, *65*, 1601–1614.
29. Effect of BF_3 on the alkylation of allylic alcohol: Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318–2325.
30. SN2′ addition to vinylic epoxide: (a) Marshall, J. A.; Andia, V. H. *J. Org. Chem.* **1987**, *52*, 1106–1113. (b) Saddler, J. C.; Fucks, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2112–2114.
31. Examples of allylic azide from allylic alcohol by the Mitsunobu reaction, see: (a) Jarvest, R. L.; Berge, J. M.; Brown, P.; Houge-Frydrych, C. S. V.; O'Hanlon, P. J.; McNair, D. J.; Pope, A. J.; Rittenhouse, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1265–1268. (b) Chandrasekhar, S.; Raza, A.; Takhi, M. *Tetrahedron: Asymmetry* **2002**, *13*, 423–428. (c) Sen, S. E.; Roach, S. L. *Synthesis* **1995**, 756–758.
32. SN2 and SN2′ allylic azidation reaction of allylic mesylate or bromide and rearrangement of allylic azide, see: (a) Hirasawa, H.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 7587–7590. (b) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Piccinelli, F.; Tolomelli, A. *Org. Lett.* **2005**, *7*, 533–536 and references cited therein.
33. Uenishi, J.; Hamada, M. *Synthesis* **2002**, 625–630.
34. Low temperature preparation of the mesylate of optically pure benzhydrol followed by nucleophilic substitution, see: Bolshan, Y.; Chen, C.-yi.; Chilenski, J. R.; Gosselin, F.; Mathre, D. J.; O'Shea, P. D.; Roy, A.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 111–114.
35. Kinetic of rearrangement of allylic azides, see: (a) Gragneux, A.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1960**, *82*, 5956–5957. (b) VanderWerf, C. A.; Heasley, V. L. *J. Org. Chem.* **1966**, *31*, 3534–3539.
36. Kirihara, M.; Takuwa, T.; Takizawa, S.; Momose, T.; Nemoto, H. *Terahedron* **2000**, *56*, 8275–8280.
37. Taguchi, T.; Kitagawa, O.; Morikawa, T.; Nishiwaki, T.; Uehara, H.; Endo, H.; Kobayashi, Y. *Tetrahedron Lett.* **1986**, *27*, 6103–6106.
38. Taguchi, T.; Kitagawa, O.; Suda, Y.; Ohkawa, S.; Hashimoto, A.; Iitaka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 5291–5294.