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SmI_2-Mediated Reduction of γ,γ-Difluoro-α,β-enoates with Application to the Synthesis of Functionalized (*Z*)-Fluoroalkene-Type Dipeptide Isosteres

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A samarium diiodide (SmI_2)-mediated reduction of γ,γ-difluoro-α,β-enoates (**15**, **29**, and **34**) was successfully applied to the synthesis of (*Z*)-fluoroalkene dipeptide isosteres (**23**, **30**, and **35**), which have served as potential dipeptide mimetics. Reduction of the γ,γ-difluoro-α,β-enoates by SmI_2 proceeded via successive two-electron transfers to form dienolate species which upon kinetically controlled trapping with *t*-BuOH yielded Xaa-Gly-type fluoroalkene isosteres exemplified by **23**, **30**, and **35**. Replacement of the *t*-BuOH kinetic trapping agent with aldehydes or ketones provided access to α-substituted fluoroalkene isosteres (**43** and **45**) through aldol reactions of Sm-dienolates with the carbonyl compounds. Of particular note, the use of the SmI_2−HCHO reagent system with chiral enoate **34** provided D-Phe-ψ[(*Z*)-CF=CH]-D/L-Ser isosteres (**45**), which could be converted to enantiomerically pure isosteres (**49**−**52**) that bore a variety of side chain functionalities at the α-position. This was achieved by a sequence of manipulations consisting of β-lactone formation followed by chromatographic separation and ring-opening with soft nucleophiles. Included in the present work is the first utilization of a Rh-catalyzed Reformatsky reaction of chiral imines for the stereoselective preparation of α,α-difluoro-β-amino acid derivatives (**28** and **33**). The appropriate choice of reagents (carbonyl compounds for kinetic trapping or ring-opening nucleophiles and imines for Reformatsky reactions) allows the presented methodology to yield various fluoroalkene isosteres possessing a wide range of side chain functionalities.

Introduction

(*Z*)-Fluoroalkene-type dipeptide isosteres **1** have served as potential dipeptide mimetics, where the peptide bond within a parent dipeptide is replaced by fluoroolefin units[1] (Figure 1). Both the fluoroalkene isosteres and their counterparts lacking fluorine substitution (disubstituted (*E*)-alkene isosteres **2**[2]) are stable against proteases, and resemble the parent peptide bonds[3] in their three-dimensional structure. On the other hand, when viewed from their electrostatic nature, the fluoroalkene isosteres **1** are more similar to peptide bonds than **2** due to the presence of the highly negative fluorine atom.[1a,b,4] Additionally, when incorporated into peptides, a trisubstituted alkene dipeptide isostere that possesses a substituent on the γ-position provides effects on the overall structure of peptides similar to that seen in native peptide bonds due to restriction of ϕ,ψ-dihedral angles.[5] This restriction in native peptides is known to be attributable to interactions between the carbonyl oxygen and other atoms, especially the side chain β-carbon.[6]

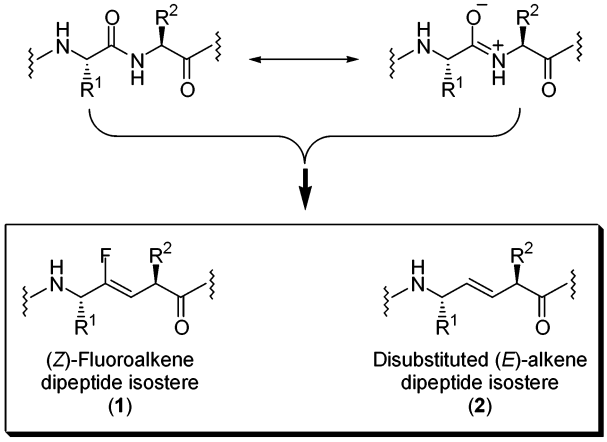

FIGURE 1. Native peptide bond and corresponding alkene isosteres.

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Because fluorine and oxygen are quite similar in their van der Waals radii (F, 1.35 Å; O, 1.40 Å) as well as being isoelectronic with each other ($2S^22P^6$),[4d] the similarity in restriction-effects mentioned above is to be expected. These qualities of fluoroalkene dipeptide isosteres have contributed to the fact that a substance P analogue containing a Phe-ψ[(*Z*)-CF=CH]-Gly unit has been shown to exhibit potency comparable to that of the natural ligand whereas the disubstituted (*E*)-alkene counterpart was significantly less potent.[1c]

Syntheses of this class of compounds have been achieved by the use of aldol reactions of α-fluoro-α,β-unsaturated aldehydes with ester enolates, followed by introduction of nitrogen functionality, or by fluoroolefination reactions of aldehydes or ketones with α-fluoroacetate derivatives.[1b−g] These synthetic methods are based on a strategy wherein the construction of fluoroalkene units is followed by derivatization of functional groups. This requires relatively long reaction sequences. During the course of our synthetic studies on nonhydrolyzable phosphoamino acids,[7] we found that γ-phosphono-γ,γ-difluoro-α,β-enoate **3** was reduced to the corresponding γ-phosphono-γ-fluoro-β,γ-enoate **4** with organocopper reagents.[8] This organocopper-mediated reduction[9] was then applied to the synthesis of (*Z*)-fluoroalkene dipeptide isosteres **6** (Figure 2).[10,11] Mechanistic investigation of the organocopper-mediated reduction of the highly electrophilic δ-amino-γ,γ-difluoro-α,β-enoates **5** led us to envision that single electron transfer (SET) from an organocopper to the substrate is responsible for the reduction.[12,13]

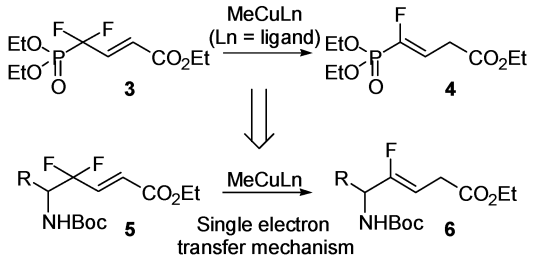

FIGURE 2. Organocopper-mediated reduction of γ-phosphono-γ,γ-difluoro-α,β-enoate.

Samarium diiodide (SmI_2)[14] has been well-recognized as a powerful one-electron reducing agent capable of meeting the diverse demands of synthetic organic chemistry.[15] Taking account of our mechanistic insight into the organocopper-mediated reduction, we speculated that SmI_2 would also be applicable to the reduction of γ,γ-difluoro-α,β-enoates to give γ-fluoro-β,γ-enoates, which could open the avenue to the synthesis of fluoroalkene dipeptide isosteres with δ-amino-γ,γ-difluoro-α,β-enoates as key intermediates (Figure 2, **5** to **6**). We present herein an examination of the feasibility of the SmI_2-mediated reduction of γ,γ-difluoro-α,β-enoates and its application to the syntheses of fluoroalkene dipeptide isosteres, including the synthesis of chiral α-functionalized (*Z*)-fluoroalkene dipeptide isosteres.

Results and Discussion

Prior to examination of the synthetic applicability of SmI_2 to preparation of the fluoroalkene isosteres, δ-siloxy-γ,γ-difluoro-α,β-enoates such as **10** were subjected to SmI_2- or organocopper-mediated reduction for comparison of these reagent systems. Requisite substrates

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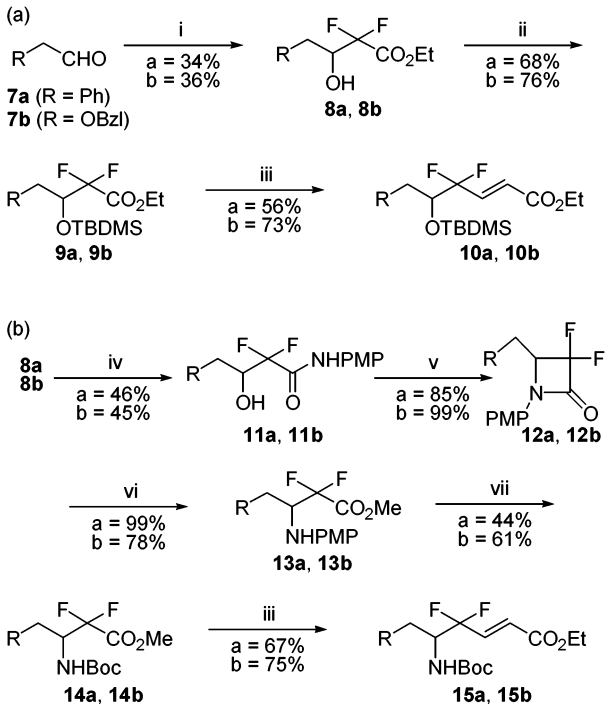
SCHEME 1[a]



[a] Reagents and conditions: (i) $BrZnCF_2CO_2Et$, THF; (ii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2; (iii) DIBAL-H, CH_2Cl_2−toluene, then $(EtO)_2P(O)CH_2CO_2Et$, LiCl, $(i\text{-}Pr)_2NEt$, MeCN; (iv) NaOH, THF−H_2O, then BOP-Cl, *p*-anisidine, $(i\text{-}Pr)_2NEt$, CH_2Cl_2; (v) Ph_3P, DEAD, THF; (vi) NaOH, THF−H_2O, then H_2SO_4, MeOH; (vii) CAN, MeCN−H_2O, then $(Boc)_2O$, THF.

were synthesized as follows (Scheme 1a): (1) Reformatsky reaction of aldehydes **7** with $BrZnCF_2CO_2Et$, followed by TBDMS protection of the resulting hydroxyl group, and (2) DIBAL-H reduction of the esters **9** to the corresponding aldehydes, followed by carbon chain elongation with Horner−Emmons olefination. Reaction of **10a** or **10b** with a cyano Gilman reagent ($Me_2CuLi{\cdot}LiCN$)[16,17] afforded the corresponding (*Z*)-*δ*-siloxy-*γ*-fluoro-*β*,*γ*-enoates[18] **16a** or **16b** with an accompanying significant amount of fluorodiene **17a** or **17b**, respectively (Table 1, entries 1 and 2). This undesirable fluorodiene formation may be attributable to the presence of hydrogen atoms that are easily abstracted by the organocopper reagent at the position adjacent to the *δ*-siloxy group. Initial attempts to reduce **10b** with SmI_2 in THF gave the desired (*Z*)-fluoroalkene in low yield (17%) with accompanying unidentified products (Table 1, entry 3). The use of SmI_2 in the presence of protic solvent has been well-documented to suppress the formation of side products resulting from unproductive pathways. Reports have indicated that *γ*,*δ*-epoxy-α,*β*-enoates undergo reductive epoxide ring opening with SmI_2 in THF in the presence of a proton source to give *δ*-hydroxy-*β*,*γ*-enoates.[19] Addition of EtOH as a proton source in the reduction of the *γ*,*γ*-difluoro-α,*β*-enoates **10** proved to improve the chemical yields (67% for **10a** and 78% for **10b**); nonetheless, a nonnegligible amount of 1,4-reduction products **18** was formed.[20]

In analogy to the proposed reaction mechanism for *γ*,*δ*-epoxy-α,*β*-enoates,[19a,b,d] a pathway via dienolates[21] **21** resulting from successive two-electron transfers is likely to be involved in the reduction of the *γ*,*γ*-difluoro-α,*β*-enoates **10** with SmI_2 in THF in the presence of a proton source (Figure 3). This proposed mechanism is probably adequate in light of the experimental observation that transfer of two electrons into the *π*-electron system adjacent to a trifluoromethyl group induces the pushing out of one of the fluorine atoms of the CF_3 group.[22] Formation of the 1,4-reduction products **18** would seem to be attributable to protonation at the *β*-position of the possible intermediate **20** to yield enolates **22**. On the basis of such a mechanism for 1,4-reductive product formation, we speculated that the use of more sterically crowded alcohols with lower acidity (e.g. *t*-BuOH) as proton sources could prevent the protonation at the *β*-carbon to give the dienolates **21**, which could be converted to the desired reductive product **16** by protonation at the α-carbon. Reaction of **10a** or **10b** with SmI_2 in THF in the presence of *t*-BuOH as the proton source (THF:*t*-BuOH = 7.3 or 7.7:0.5, v/v) at 0 °C for 60 min proceeded quantitatively to yield the desired *γ*-fluoro-*β*,*γ*-enoates **16a** or **16b** in 92% or 90% isolated yield, respectively, without any detectable formation of 1,4-reductive product or fluorodiene (Table 1, entries 6 and 7).[23] Addition of a stoichiometrical amount of *t*-BuOH was sufficient for the clean SmI_2-mediated conversion of **10** to **16**. Having ascertained the reductive conditions for use of SmI_2 with *γ*,*γ*-difluoro-α,*β*-enoates, we next applied the SmI_2-mediated reductive protocol to the synthesis of

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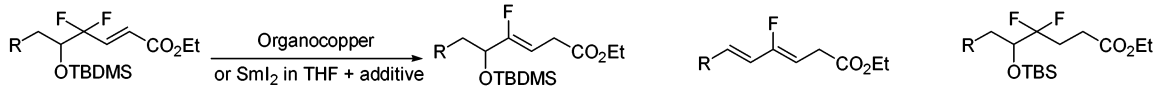
TABLE 1. Reduction of δ-Siloxy-γ,γ-difluoro-α,β-enoates with Organocopper or SmI_2



10a (R = Ph) **10b** (R = OBzl) **16a** (R = Ph) **16b** (R = OBzl) **17a** (R = Ph) **17b** (R = OBzl) **18a** (R = Ph) **18b** (R = OBzl)

entry	substrate	reagent (equiv, solvent, additive)	condition	products (isolated yield %)
1	**10a**	$Me_2CuLi{\cdot}LiCN^a$ (4 equiv, THF:Et_2O = 4:1)	−78 °C, 10 min	**16a** (59), **17a** (10)[b]
2	**10b**	$Me_2CuLi{\cdot}LiCN^a$ (4 equiv, THF:Et_2O = 4:1)	−78 °C, 10 min	**16b** (36), **17b** (31)
3	**10b**	SmI_2 (6 equiv, THF)	0 °C, 60 min	**16b** (17)[c]
4	**10a**	SmI_2 (6 equiv, THF:EtOH = 7.7:0.5)	0 °C, 60 min	**16a** (67), **18a** (25)[b]
5	**10b**	SmI_2 (6 equiv, THF:EtOH = 7.3:0.5)	0 °C, 60 min	**16b** (78), **18b** (15)[b]
6	**10a**	SmI_2 (6 equiv, THF:*t*-BuOH = 7.7:0.5)	0 °C, 60 min	**16a** (92)
7	**10b**	SmI_2 (6 equiv, THF:*t*-BuOH = 7.3:0.5)	0 °C, 60 min	**16b** (90)
8	**10a**	SmI_2 (6 equiv, THF + 1.5 equiv. *t*-BuOH)	0 °C, 60 min	**16a** (94)
9	**10b**	SmI_2 (6 equiv, THF + 1.5 equiv. *t*-BuOH)	0 °C, 60 min	**16b** (86)

[a] In the presence of Li salts (LiCl and LiBr). [b] Obtained as mixtures. The ratios were determined by ^{1}H NMR. [c] No starting material. Several unidentified compounds were formed.

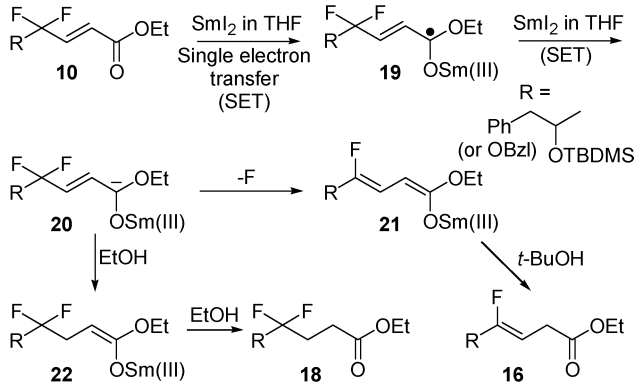


FIGURE 3. Possible mechanism of the reaction of γ,γ-difluoro-α,β-enoates with SmI_2.

fluoroalkene dipeptide isosteres in comparison with the organocopper-mediated method.

Requisite substrates **15a** and **15b** were synthesized in a nonstereoselective manner as follows (Scheme 1b): (1) hydrolysis of **8a** or **8b** and subsequent amide formation with *p*-anisidine with the aid of bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOP-Cl);[24] (2) conversion of the hydroxyl group to amine functionality utilizing a sequence of reactions consisting of intramolecular Mitsunobu reaction,[25] hydrolysis of the resulting β-lactams **12**, and esterification of the carboxylic acids; (3) deprotection of the PMP (*p*-methoxyphenyl) group of **13** followed by Boc-reprotection; and (4) carbon chain elongation by DIBAL-H reduction of the Boc-protected β-amino acid esters **14** and subsequent Horner−Emmons olefination with triethyl phosphonoacetate. Reduction of **15a** or **15b** with SmI_2 or organocopper for the preparation of the fluoroalkene isosteres is summarized in Table 2. Both the reaction with the cyano Gilman reagent ($Me_2CuLi{\cdot}LiCN$ at −78 °C for 10 min) and that with SmI_2-*t*-BuOH (7.7 or 7.3:0.5, v/v, 0 °C for 60 min) proceeded quantitatively to yield the desired (*Z*)-fluoroalkene isosteres in high chemical yields (slightly higher yields in the case of the SmI_2-mediated method). The resulting fluoroalkene isosteres were obtained as racemates due to the nonstereoselective synthesis of precursor γ,γ-difluoro-α,β-enoates **15**. On the basis of these preliminary experiments, synthesis of chiral fluoroalkene isosteres was envisioned via stereoselective preparation of the α,α-difluoro-β-amino acids as outlined in the following.

Recent growing interest in both the medicinal and the synthetic organic chemistry of fluororinated β-amino acids[26] has led to the development of methodologies for their asymmetric synthesis.[27,28] Published methods utilizing the addition of a Reformatsky-type reagent ($BrZnCF_2$-CO_2Et) to chiral imines[27] prompted us to use a similar type of reaction for the construction of our chiral units. Recently, Honda et al. reported a one-pot preparation of chiral β-amino esters by a rhodium-catalyzed three-component coupling reaction, where ethyl bromoacetate is added to chiral aldimines with complete diastereoselectivity under mild reaction conditions (0 °C) in the presence of Wilkinson's catalyst and diethylzinc.[29,30] The chiral aldimines were prepared from aldehydes and an *O*-protected phenylglycinol derivative in situ in the presence of molecular sieves. Honda's protocol was of note because simple operations with mild reaction conditions give β-amino acid esters in contrast to the fact that

(23) Proton sources have been reported to exert an influence on the regiochemical and stereochemical outcome of SmI_2-mediated reduction. see: (a) Yoshida, A.; Mikami, K. *Synlett*. **1997**, 1375−1376. (b) Yoshida, A.; Hanamoto, T.; Inanaga, J.; Mikami, K. *Tetrahedron Lett*. **1998**, *39*, 1777−1780. In addition to the steric hindrance of *t*-BuOH, the low acidic nature of *t*-BuOH as compared with that of EtOH would also contribute to slow protonation at the β-carbon of **20**, which results in the preferential conversion of **20** to **16** via the dienolate **21**.

(24) Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernandez-Lizarbe, J. R.; Zugaza-Bibao, A. *Synthesis* **1980**, 547−551.

(25) Nakayama, K.; Kawato, H. C.; Inagaki, H.; Nakajima, R.; Kitamura, A.; Someya, K.; Ohta, T. *Org. Lett*. **2000**, *2*, 977−980.

(26) For reviews on fluorinated amino acids, see: (a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123−3197. (b) Kukhar', V. P.; Soloshonok, V. A., Eds. *Fluorine-containing Amino Acids*; John Wiley & Sons: New York, 1994.

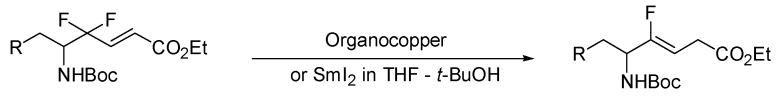
(27) (a) Marcotte, S.; Pannecoucke, X.; Feasson, C.; Quirion, J.-C. *J. Org. Chem*. **1999**, *64*, 8461−8464. (b) Staas, D. D.; Savage, K. L.; Hormnick, C. F.; Tsou, N. N.; Ball, R. G. *J. Org. Chem*. **2002**, *67*, 8276−8279.

(28) For reports on use of difluoroketenesilylacetal, see: (a) Iseki, K.; Kuroki, Y.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 10271−10280. (b) Iseki, K. *Tetrahedron* **1998**, *54*, 13887−13914.

(29) Honda, T.; Wakabayashi, H.; Kanai, K. *Chem. Pharm. Bull*. **2002**, *50*, 307−308.

(30) Adrian, J. C., Jr.; Snapper, M. L. *J. Org. Chem*. **2003**, *68*, 2143−2150.

TABLE 2. Reduction of δ-Amino-γ,γ-difluoro-α,β-enoates with Organocopper or SmI_2



15a (R = Ph)
15b (R = OBzl)

23a (R = Ph)
23b (R = OBzl)

entry	substrate	reagent (equiv, solvent)	condition	product (isolated yield %)
1	**15a**	$Me_2CuLi{\cdot}LiCN$[a] (4 equiv, THF:Et_2O = 4:1)	−78 °C, 10 min	**23a** (84)
2	**15b**	$Me_2CuLi{\cdot}LiCN$[a] (4 equiv, THF:Et_2O = 4:1)	−78 °C, 10 min	**23b** (89)
3	**15a**	SmI_2 (6 equiv, THF:*t*-BuOH = 7.7:0.5)	0 °C, 60 min	**23a** (92)
4	**15b**	SmI_2 (6 equiv, THF:*t*-BuOH = 7.3:0.5)	0 °C, 60 min	**23b** (94)

[a] In the presence of Li salts (LiCl and LiBr).

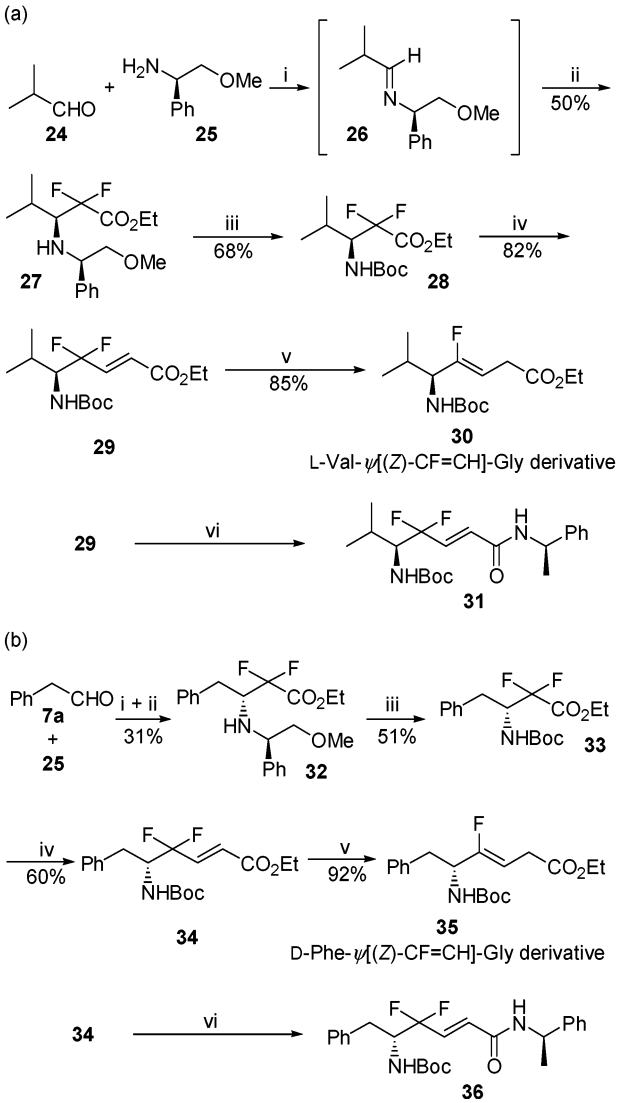
addition of Reformatsky reagents to imines usually yields β-lactam derivatives.[27a] Therefore, we attempted to apply this method to the asymmetric synthesis of requisite α,α-difluoro-β-amino acid derivatives such as **14** by replacement of ethyl bromoacetate with ethyl bromodifluoroacetate. Initially the stereoselective synthesis of a L-Val-Gly-type fluoroalkene dipeptide isostere **30** was envisioned (Scheme 2-(a)).

Successive addition of Wilkinson's catalyst, ethyl bromodifluoroacetate, and diethylzinc to the chiral aldimine **26** prepared from isobutyraldehyde **24** and the methyl ether of (*R*)-phenyl glycinol[31] **25** with the aid of activated molecular sieves resulted in the diastereoselective formation of the (*S*)-α,α-difluoro-β-amino ester **27** in moderate yield.[32] The chiral auxiliary was then removed by hydrogenolysis with $Pd(OH)_2/C$-H_2 in EtOH. The resulting amine compound was Boc protected with $(Boc)_2O$ in THF under refluxing conditions to yield derivative **28**, which was converted to γ,γ-difluoro-α,β-enoate **29** as a substrate for the SmI_2-mediated reduction in a manner identical with that employed for the synthesis of **15**. Establishment of chirality as being of the (*S*)-configuration was achieved as follows: (1) hydrolysis of ethyl ester **29**; (2) condensation with (*R*)-methylbenzylamine; and (3) X-ray analysis of crystallized sample **31**. Reaction of **29** with SmI_2 in THF in the presence of *t*-BuOH proceeded quantitatively to afford L-Val-Gly-type fluoroalkene isostere **30** in 85% isolated yield.

Transition state model **37**[29,33] can be used to rationalize the reaction outcome of the addition of the Reformatsky-type reagent to the chiral aldimine **26** (Figure 4). According to this model, the zinc enolate attacks from the less-hindered *Re* face of the imine to furnish the (*S*)-α,α-difluoro-β-amino ester **27**.

Next, the synthesis of the chiral Phe-Gly-type isostere **35** was undertaken, which required the condensation of phenylacetaldehyde **7a** and the chiral amine **25** (Scheme 2b). The analogous *p*-toluenesulfinyl imine has been reported to favor the corresponding tautomeric form (enamine) rather than the aldimine.[34,35] In addition, competitive α-deprotonation can be problematic during addition of organometallic reagents to imines prepared from phenylacetaldehyde. A one-pot reaction consisting

SCHEME 2[a]



[a] Reagents and conditions: (i) molecular sieves 3Å, THF; (ii) $BrCF_2CO_2Et$, Et_2Zn, $RhCl(PPh_3)_3$, THF−hexane; (iii) $Pd(OH)_2$, H_2, EtOH, then $(Boc)_2O$, THF; (iv) DIBAL-H, CH_2Cl_2−toluene, then $(EtO)_2P(O)CH_2CO_2Et$, LiCl, $(i\text{-}Pr)_2NEt$, MeCN; (v) SmI_2, *t*-BuOH, THF; (vi) 1 M LiOH (aq), THF, then (*R*)-methylbenzylamine, 1-hydroxybenzotriazole, 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide, $(i\text{-}Pr)_2NEt$, THF.

(31) Smith, A. B., III; Yager, K. M.; Phillips, B. W.; Taylor, C. M. *Org. Synth.* **1998**, *75*, 19−30.

(32) In our experiments, flash chromatographical purification of crude **27** (or **32**) did not afford another diastereomer even though the possibility of formation of a diastereomer cannot be completely ruled out.

(33) Mokhallalati, M. K.; Wu, M.-J.; Pridgen, L. N. *Tetrahedron Lett.* **1993**, *34*, 47−50.

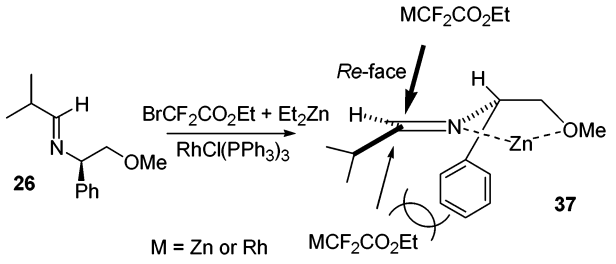


FIGURE 4. Proposed mechanism of addition to chiral imine **26**.

of a chiral aldimine (prepared from **25** and **7a**) ethyl bromodifluoroacetate, Wilkinson's catalyst, and diethylzinc in THF at 0 °C for 30 min proceeded with high diastereoselectivity to give diastereomerically pure α,α-difluoro-*β*-amino acid derivative **32** in 31% isolated yield.[32] Compound **32** was converted to the requisite substrate **34** for the SmI_2-mediated reduction in a manner identical with that used for transformation of **27** to **29**. To determine the absolute configuration at the *δ*-carbon of **34**, compound **34** was converted to the crystalline amide **36** by a similar sequence of reactions used for the preparation of **31**. X-ray crystallographic analysis of **36** showed that the absolute configuration is *R*. This stereo preference is opposite to what was observed when isobutyraldehyde was used. Although the origin of reversal of the stereoselectivity was not thoroughly examined, the following factors could explain this phenomenon (Figure 5).

As mentioned above, imines prepared from phenylacetaldehyde have a tendency to exist in tautomeric equilibrium between imines **38** and enamines **39** or **40** due to the presence of the phenylacetaldehyde aromatic nucleus. The imine−enamine equilibrium could facilitate the interconversion between two possible reactive imine conformers **38*E*** and **38*Z*** (giving zinc-chelated imines **41** and **42**, respectively).[36] Even though other factors cannot be excluded, one possible explanation for the observed reaction outcome is that addition of the incoming Zn-enolate to the *Si* face of intermediate **42** is likely to be favored either kinetically or thermodynamitically to yield the compound possessing the observed absolute configuration. At present, it is unclear whether the reaction proceeds under kinetic or thermodynamic control.

Enantiomerically pure *γ*,*γ*-difluoro-α,*β*-enoate **34** was subjected to reaction with SmI_2-*t*-BuOH in THF at 0 °C for 60 min to afford chiral D-Phe-Gly-type fluoroalkene dipeptide isostere (D-Phe-*ψ*[(*Z*)-CF=CH]-Gly) **35** in 92% isolated yield. Taken together, the above-described SmI_2-*t*-BuOH reduction protocols were useful for the synthesis of chiral Xaa-Gly-type fluoroalkene isosteres. Introduction of an α-substituent into the isosteres is planned based on the same SmI_2-mediated reduction.

As mentioned above, formation of dienolate species in the SmI_2-mediated reduction of *γ*,*γ*-difluoro-α,*β*-enoates appears to be involved. Trapping of the dienolates with electrophiles, with the exception of proton electrophiles, is envisioned to result in the formation of α-substituted isosteres. In one instance, Molander et al. reported the trap of the Sm-dienolate derived from a *γ*,*δ*-epoxy-α,*β*-enoate with MeI as an electrophile, albeit in relatively low yields (39%).[19a] We also carried out the reaction of *γ*,*γ*-difluoro-α,*β*-enoate **34** with SmI_2 in THF in the presence of BzlBr; however, no α-alkylated isostere was obtained except for reduction product and several unidentified compounds (Table 3, entry 1). Thereupon, examination of electrophiles as possible trapping agents was extended to include carbonyl compounds such as aldehydes and ketones (Table 3, entries 2−4). One representative example of the SmI_2-mediated intermolecular coupling with this type of substrate combination (alkenes and aldehydes or ketones) is the reductive coupling between carbonyl compounds (aldehydes or ketones) and activated alkenes such as α,*β*-enoates.[37] In this reaction, ketyls derived from reduction of aldehydes or ketones with SmI_2 couple to the *β*-position of the α,*β*-enoates to yield *γ*-lactone derivatives. Kinetic electrophilic trapping of intermediates resulting from *γ*,*γ*-difluoro-α,*β*-enoates with SmI_2 can result in clean conversion of substrates to the desired reduction products. With this in mind, we attempted the SmI_2-mediated reduction of the *γ*,*γ*-difluoro-α,*β*-enoate **34** in the presence of aldehydes or ketones with the intention of nucleophilic attack of the α-carbon in the intermediary conjugated Sm-dienolates onto the carbonyl compounds.[38,39] This would allow coupling of ketyls derived from carbonyl compounds onto the *β*-carbon.

Reaction of enoate **34** with SmI_2 (3 equiv) in THF in the presence of acetone (3 equiv) at 0 °C for 60 min proceeded smoothly to yield α-substituted aldol compound **43** as a mixture of α-carbon diastereomers in 82% combined yield. No *β*-substituted product was observed. Although an in-depth mechanistic investigation of the above coupling reaction was not pursued, the fact that α-aldol coupling products were unambiguously obtained in high yields supports the proposed reaction mechanism, where the *γ*,*γ*-difluoro-α,*β*-enoates rather than carbonyl compounds are preferentially reduced with SmI_2 in THF to form dienolates such as **21**, which react with ketones at their α-position.[38,40] The use of diethyl dicarbonate as an electrophile allowed a Claisen-type condensation to give the α-ethoxycarbonyl fluoroalkene isostere **44**.

Synthesis of α-hydroxymethylated fluoroalkene isosteres is of synthetic value with respect to the prepara-

(34) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem*. **1997**, *62*, 2555−2563.

(35) Successful example of addition to the imine prepared from phenylacetaldehyde, see: Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883−8904.

(36) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron*: *Asymmetry* **1992**, *3*, 459−505 and references cited herein.

(37) (a) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun*. **1986**, 624−625. (b) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1669−1675. (c) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, 111, 8236−8246. (d) Fukuzawa, S.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482−1483. (e) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G.-Q. *J. Org. Chem*. **2001**, *66*, 3953−3962.

(38) Presumably, because the *π*-electron density is higher at the α-carbon than the *γ*-carbon, extended dienolate normally reacts with alkylating agents to produce α-substituted-*β*,*γ*-unsaturated compounds. see: (a) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 3, pp 1−63. (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: New York, 1976.

(39) SmI_2-mediated conjugated reduction/intramolecular aldol reactions of compounds possessing α,*β*-enoate and ketone moieties have recently been reported, see: (a) Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett*. **2002**, *4*, 2345−2347. (b) Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett*. **2003**, *5*, 4811−4814.

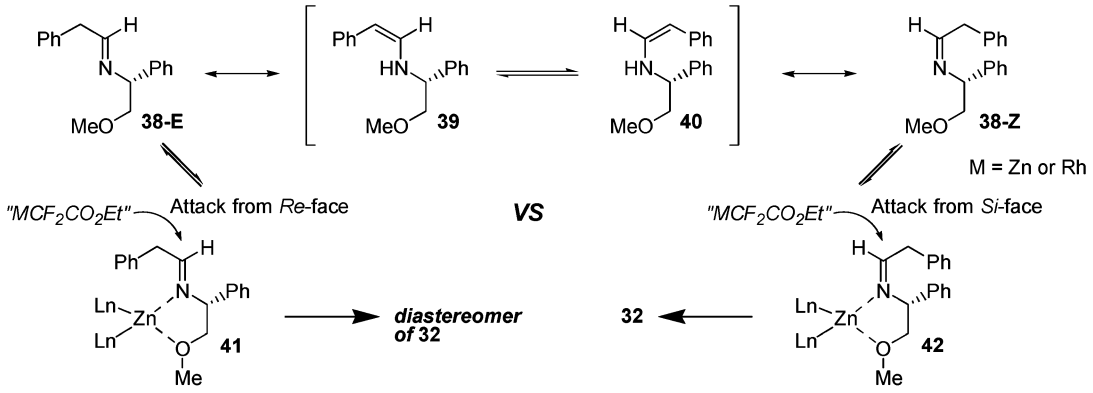
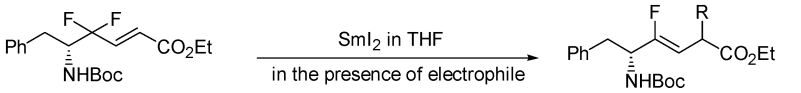


FIGURE 5. A plausible explanation for reversal of the stereochemical outcome with an imine derived from phenylacetaldehyde.

TABLE 3. Reduction of γ,γ-Difluoro-α,β-enoate with SmI_2 in the Presence of Electrophiles



34

43 (R = $C(CH_3)_2OH$)
44 (R = CO_2Et)
45 (R = CH_2OH)

entry	electrophile (equiv)	reagent (equiv, solvent)	condition	products[a] (isolated yield %)
1	BzlBr (3 equiv)	SmI_2 (6 equiv, THF)	0 °C, 60 min	*b*
2	CH_3COCH_3 (3 equiv)	SmI_2 (3 equiv, THF)	0 °C, 60 min	**43** (82)
3	$(EtOCO)_2O$ (5 equiv)	SmI_2 (6 equiv, THF)	0 °C, 60 min	**44** (76)
4	HCHO (6 equiv)[c]	SmI_2 (3 equiv, THF)	0 °C, 60 min	**45** (65)

[a] Combined yield of diastereomers except for **44**. [b] Unidentified products were formed. [c] Formaldehyde complex was prepared from *s*-trioxane (2 equiv), 2,6-diphenylphenol (12 equiv), and Me_3Al (6 equiv) in CH_2Cl_2−hexane.

tion of several α-functionalized isosteres because the hydroxymethyl group can be easily converted to other functional groups. For such purposes, trapping of the dienolates with formaldehyde may be suitable; however, addition of commercially available formalin to the SmI_2-mediated reduction resulted in failure to furnish Xaa-Gly-type isosteres. This was due to the predominant quenching with H_2O derived from the formalin solution. Yamamoto et al. reported that formaldehyde can be generated under aprotic conditions by treatment of readily available *s*-trioxane with methylaluminum bis(2,6-diphenylphenoxide) (MAPH) to stabilize formaldehyde as a MAPH complex.[41] The resulting complex is useful as a stable source of reactive formaldehyde in aprotic media for reactions with a variety of nucleophiles such as enolates and olefins. This work prompted us to use the formaldehyde−MAPH complex as a trapping reagent for dienolates derived from the SmI_2-mediated reduction of **34**. Reaction with SmI_2 (3 equiv) in THF at 0 °C for 60 min of a mixture of **34** and the formaldehyde−MAPH complex (6 equiv), prepared as CH_2Cl_2−hexane solution, gave a diastereomeric mixture of α-hydroxymethyl fluoroalkene isosteres (D-Phe-ψ[(*Z*)-CF=CH]-L/D-Ser) **45** in 65% isolated yield (Table 3, entry 4). As with the enoate **34**, essentially no stereoselectivity was noted for these coupling reactions with either acetone or formaldehyde. It does not appear that the distal substituent on the δ-carbon has any stereodirecting effect with respect to the incoming electrophile. Enzyme-catalyzed enantioselective hydrolysis of esters is an attractive means to obtain chiral amino acid derivatives. However, attempted selective hydrolysis of the diastereomeric mixture **45** met with failure.

To transform the hydroxymethyl group to another side chain functionality, the Phe-Ser-type isostere **45** was subjected to saponification followed by intramolecular Mitsunobu reaction to afford β-lactone derivatives **47** and **48**, which were susceptible to soft nucleophiles[42] (Scheme 3). Fortunately, at this stage, diastereomeric β-lactones **47** and **48** were easily separable by flash chromatography on silica gel. Reaction of β-lactone derivatives derived from protected serine with a variety of soft nucleophiles such as thiols and organocopper reagents has been reported to provide access to various *N*-protected amino acids that result from alkyl−oxygen cleavage.[42] Treatment of each purified lactone **47** and **48** with isopropyl Grignard reagent in the presence of $CuBr\cdot Me_2S$ in THF, followed by $TMSCHN_2$ treatment,[43] proceeded with cleavage of the alkyl−oxygen bond to give D-Phe-ψ[(*Z*)-CF=CH]-Leu isosteres (**49** and **51**) in 40% and 66%

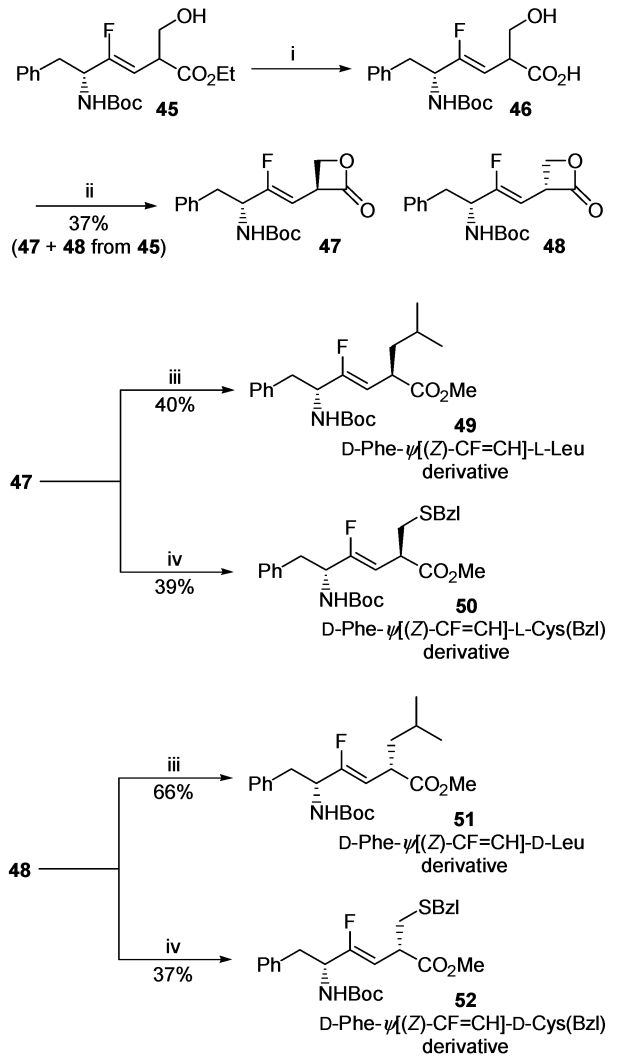
(40) For samarium enolate formation in the presence of aldehydes or ketones, see: (a) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036−8045. (b) Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. *J. Org. Chem.* **2000**, *65*, 1702−1706. (c) Ricci, M.; Blaksjær, P.; Skrydstrup, T. *J. Am. Chem. Soc.* **2000**, *122*, 12413−12421.

(41) Maruoka, K.; Concepcion, A. B.; Murase, N.; Oishi, M.; Hirayama, N.; Yamamoto, Y. *J. Am. Chem. Soc.* **1993**, *115*, 3943−3949.

(42) For the synthesis of β-lactones derived from amino acids and their application, see: (a) Pansare, S. V.; Huyer, G.; Arnold, L. D.; Vederas, J. C. *Org. Synth.* **1992**, *70*, 1−28. (b) Smith, N. D.; Goodman, M. *Org. Lett.* **2003**, *5*, 1035−1037.

(43) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475−1478

SCHEME 3[a]



[a] Reagents and conditions: (i) 1 M LiOH (aq), THF; (ii) Ph_3P, DEAD, THF; (iii) *i*-PrMgCl, CuBr·Me_2S, Me_2S, THF, then TMSCHN_2, MeOH, benzene; (iv) BzlSH, DMF, then TMSCHN_2, MeOH, benzene.

yields, respectively, without loss of chirality. Reaction of **47** and **48** with benzyl thiol in DMF, followed by esterification, also proceeded in a similar manner to afford D-Phe-ψ[(*Z*)-CF=CH]-Cys(Bzl) isosteres **50** and **52**, respectively.

The absolute configurations of the alkyl groups at the α-position in acyclic α-alkyl-(*E*)-β,γ-enoates can be determined by CD measurement with use of an empirical rule.[44] According to this rule, 2*S*-compounds corresponding to the D-series provide a positive Cotton effect, while 2*R*-compounds (L-series) yield a negative Cotton effect. By showing negative Cotton effects, compounds **49** and **50** were assigned (2*R*)-configurations, which correspond to (D,L)-type isosteres (D-Phe-Ψ[(*Z*)-CF=CH]-L-Leu (or L-Cys(Bzl)). Similarly, on the basis of their positive Cotton effects, compounds **51** and **52** were assigned (2*S*)-configurations, corresponding to (D,D)-type isosteres.

In conclusion we have devised facile methodologies for the synthesis of (*Z*)-fluoroalkene dipeptide isosteres which are potential dipeptide mimetics having structural as well as electrostatic similarity to the parent peptide bonds. The SmI_2-mediated reduction of γ,γ-difluoro-α,β-enoates was utilized to provide access to this class of mimetics. Our previous finding that γ,γ-difluoro-α,β-enoates can be reduced to γ-fluoro-δ,γ-enoates by organocopper reagents via successive single-electron-transfer processes led to our current development of the SmI_2-mediated approach toward the synthesis of (*Z*)-fluoroalkene dipeptide isosteres. By proceeding in an S_N2'-fashion, the SmI_2 reduction is likely to involve formation of dienolates, which upon kinetic trapping with proton sources (*t*-BuOH) yields Xaa-Gly-type fluoroalkene isosteres. Additionally, trapping of reduction intermediate with ketones or aldehydes affords α-substituted fluoroalkene isosteres due to the fact that highly electrophilic γ,γ-difluoro-α,β-enoates are more quickly reduced than coexisting carbonyl compounds. Furthermore, one-pot rhodium-catalyzed Reformatsky reactions of chiral aldimines and bromoacetate derivatives were successfully extended to the asymmetric synthesis of α,α-difluoro-β-amino esters, which were then subjected to the further preparation of chiral Xaa-Gly- or α-hydroxymethylated-type fluoroalkene isosteres with SmI_2-*t*-BuOH or SmI_2-HCHO protocols, respectively. Here, it is worth noting that access to various fluoroalkene isosteres possessing a wide variety of side chain functional group may be possible depending on the choice of both the aldehydes for imine formation and kinetic trapping by electrophiles or ring-opening by nucleophiles in the case of the β-lactones. Both the SmI_2-*t*-BuOH and SmI_2-carbonyl compound systems may have great synthetic applicability not only to the γ,γ-difluoro-α,β-enoates but also to other α,β-enoates possessing leaving groups at the γ-position.[45] Along this line, we are currently exploring the synthetic potential of these reaction systems. Synthetic applications of the SmI_2-mediated reactions and biological/structural evaluation of the fluoroalkene isosteres will be reported in due course.

Experimental Section

General Methods. Tetrahydrofuran (THF) was freshly distilled from sodium−benzophenone ketyl radical under a nitrogen atomosphere immediately prior to use. All reactions were conducted under a positive pressure of argon with oven-dried glassware. Melting points are uncorrected. Chemical shifts of the compounds, of which ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, are reported in parts per million downfield from Me_4Si (s = singlet, d = doublet, dd = double doublet, ddd = doublet of double doublet, t = triplet, m = multiplet). For flash chromatographies, mixtures of silica gel 60 H (silica gel for TLC, Merck) and Wakogel C-200 (silica gel for column chromatography, Wako) were used.

Ethyl 2,2-Difluoro-3-hydroxy-4-phenylbutanoate (8a). To a stirred suspension of Zn dust (5.7 g, 86.8 mmol), activated according to published procedure,[46] in THF (50 mL) was slowly added a solution of ethyl bromodifluoroacetate (14.7 g, 72.3 mmol) in THF (30 mL) at room temperature under argon. After additional stirring for 30 min, a solution of the aldehyde **7a**

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(10.0 g, 83.2 mmol) in THF (30 mL) was added to the above solution. The reaction mixture was stirred at 65 °C for 3 h, quenched at 0 °C by addition of aqueous 1 N HCl, and extracted with Et_2O. The extract was washed with 1 N HCl and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:5) gave the title compound **8a** (6.9 g, 34% yield) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.36 (t, J = 7.1 Hz, 3H), 2.13 (d, J = 5.9 Hz, 1H), 2.83 (dd, J = 14.2, 10.1 Hz, 1H), 3.08 (dd, J = 14.2, 2.7 Hz, 1H), 4.22−4.38 (m, 1H), 4.34 (q, J = 7.1 Hz, 2H), 7.05−7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 35.5, 63.0, 72.4, 114.0, 126.7, 128.4, 129.1, 136.0, 163.0; HRMS (FAB), *m*/*z* calcd for $C_{12}H_{15}F_2O_3$ (MH^+) 245.0989, found 245.0994.

Ethyl 3-[(*tert*-Butyl)dimethylsiloxy]-2,2-difluoro-4-phenylbutanoate (9a). To a solution of the ester **8a** (1.8 g, 8.03 mmol) in CH_2Cl_2 (11 mL) were added 2,6-lutidine (3.7 mL, 32.1 mmol) and TBDMSOTf (3.7 mL, 16.1 mmol) at 0 °C under argon. After 2 h, the reaction mixture was extracted with EtOAc. The extract was washed with 5% $NaHCO_3$, 1 N HCl, and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:20) gave the title compound **9a** (1.8 g, 68% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.50 (s, 3H), −0.06 (s, 3H), 0.77 (s, 9H), 1.37 (t, J = 7.1 Hz, 3H), 2.80 (dd, J = 13.9, 9.5 Hz, 1H), 3.06 (dd, J = 13.9, 3.2 Hz, 1H), 4.26−4.38 (m, 3H), 7.18−7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, −5.1, 13.9, 17.9, 25.5, 37.8, 62.6, 74.6, 114.6, 126.4, 128.0, 129.4, 136.8, 163.0; HRMS (FAB), *m*/*z* calcd for $C_{18}H_{21}F_2O_3Si$ (MH^+) 359.1854, found 359.1864.

Ethyl (2*E*)-5-[(*tert*-Butyl)dimethylsiloxy]-4,4-difluoro-6-phenylhex-2-enoate (10a). To a solution of the ester **9a** (1.8 g, 5.02 mmol) in CH_2Cl_2 (6 mL) was added dropwise a solution of DIBAL-H in toluene (1.0 M, 6.0 mL, 6.03 mmol) at −78 °C under argon, and the mixture was stirred for 30 min. The reaction was quenched with saturated citric acid and extracted with Et_2O. The extract was washed with saturated citric acid and brine and dried over $MgSO_4$. Concentration under reduced pressure gave an oily aldehyde, which was used immediately in the next step without further purification. To a stirred suspension of LiCl (255 mg, 6.02 mmol) in MeCN (8 mL) under argon were added $(EtO)_2P(O)CH_2CO_2Et$ (1.19 mL, 6.02 mmol) and $(i\text{-}Pr)_2NEt$ (0.96 mL, 5.52 mmol) at 0 °C. After 20 min, the above aldehyde in MeCN (12 mL) was added to the mixture at 0 °C, and the mixture was stirred at room temperature for 4 h. The mixture was extracted with Et_2O, and the extract was washed with 0.5 N HCl and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:20) gave the title compound **10a** (1.1 g, 56% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.54 (s, 3H), −0.07 (s, 3H), 0.77 (s, 9H), 1.33 (t, J = 7.2 Hz, 3H), 2.55 (dd, J = 13.6, 9.9 Hz, 1H), 2.96 (d, J = 13.6 Hz, 1H), 4.05−4.13 (m, 1H), 4.26 (q, J = 7.2 Hz, 2H), 6.33 (d, J = 15.9 Hz, 1H), 6.91 (td, J = 15.2, 9.9 Hz, 1H), 7.15−7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6, −4.9, 14.1, 17.9, 25.6, 38.3, 61.0, 75.8, 121.9, 126.0, 126.4, 128.1, 129.6, 136.4, 136.9, 164.6; HRMS (FAB), *m*/*z* calcd for $C_{20}H_{31}F_2O_3Si$ (MH^+) 385.2010, found 385.2006.

***N*-(4-Methoxyphenyl)-2,2-difluoro-3-hydroxy-4-phenylbutanamide (11a).** To a solution of the ester **8a** (4.5 g, 18.4 mmol) in THF (20 mL) was added 1 N NaOH (20.3 mL, 20.3 mmol) at room temperature. The reaction mixture was stirred for 3 h, acidified with 3 N HCl, and extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure gave a pale yellow oil, which was dissolved in CH_2Cl_2 (30 mL). To the solution were added successively $(i\text{-}Pr)_2NEt$ (8.0 mL, 46.0 mmol), *p*-anisidine (3.4 g, 27.6 mmol), and BOP-Cl (7.0 g, 27.6 mmol) at room temperature with additional stirring overnight. The mixture was extracted with EtOAc, and the extract was washed with 5% $NaHCO_3$, 1 N HCl, and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:5) gave the title compound **11a** (2.8 g, 46% yield) as a colorless powder: mp 135−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (d, J = 5.2 Hz, 1H), 2.87 (dd, J = 14.2, 10.3 Hz, 1H), 3.11 (d, J = 13.7 Hz, 1H), 3.80 (s, 3H), 4.38−4.50 (m 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.23−7.36 (m, 5H), 7.47 (d, J = 8.8 Hz, 2H), 8.01 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.6, 55.5, 72.1, 114.2, 115.3, 122.0, 126.8, 128.5, 128.7, 129.3, 136.3, 157.2, 161.0. Anal. Calcd for $C_{17}H_{17}F_2NO_3$: C, 63.54; H, 5.33; N, 4.36. Found: C, 63.51; H, 5.37; N, 4.30.

***N*-(4-Methoxyphenyl)-3-benzyl-2,2-difluoropropano-3-lactam (12a).** To a solution of Ph_3P (3.4 g, 12.9 mmol) and the amide **11a** (2.7 g, 8.60 mmol) in THF (20 mL) was added a solution of DEAD in toluene (40%, 5.1 mL, 11.2 mmol) at 0 °C under argon. After 1.5 h, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography over silica gel with EtOAc−*n*-hexane (1:8) to give the title compound **12a** (2.2 g, 85% yield) as colorless crystals: mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (dd, J = 14.9, 9.3 Hz, 1H), 3.26 (d, J = 12.9 Hz, 1H), 3.81 (s, 3H), 4.59−4.66 (m, 1H), 6.89 (d, J = 9.0 Hz, 2H), 7.23−7.36 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.0, 55.5, 66.5, 114.6, 119.7, 120.0, 127.2, 128.2, 128.7, 128.8, 135.1, 156.7, 157.3. Anal. Calcd for $C_{17}H_{15}F_2NO_2$: C, 67.32; H, 4.98; N, 4.62. Found: C, 67.37; H, 5.05; N, 4.45.

Methyl 2,2-Difluoro-3-[*N*-(4-methoxyphenyl)amino]-4-phenylbutanoate (13a). To a solution of the lactam **12a** (2.2 g, 7.29 mmol) in THF (10 mL) was added 1 N NaOH (7.6 mL, 7.60 mmol) at room temperature. After 2 h, the mixture was concentrated under reduced pressure to give an oily residue, which was dissolved in MeOH (80 mL). To the solution was added concentrated H_2SO_4 at room temperature. The reaction mixture was stirred for 3 h under reflux and extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:8) gave the title compound **13a** (2.4 g, 99% yield) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84 (dd, J = 14.2, 8.6 Hz, 1H), 3.16 (dd, J = 14.3, 4.8 Hz, 1H), 3.67 (s, 3H), 3.70 (s, 3H), 4.16−4.28 (m, 1H), 6.45 (d, J = 9.0 Hz, 2H), 6.66 (d, J = 8.8 Hz, 2H), 7.16−7.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.8, 53.1, 55.5, 60.2, 114.3, 115.4, 126.4, 128.1, 129.1, 136.3, 139.7, 152.6, 164.0; HRMS (FAB), *m*/*z* calcd for $C_{18}H_{19}F_2NO_3$ (M^+) 335.1333, found 335.1340.

Methyl 3-[*N*-(*tert*-Butoxycarbonyl)amino]-2,2-difluoro-4-phenylbutanoate (14a). To a solution of the ester **13a** (400 mg, 1.19 mmol) in MeCN (7 mL) was added a solution of CAN (1.96 g, 3.58 mmol) in H_2O (5 mL) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C and then at room temperature for 3 h. To the reaction mixture was added 3-mercaptopropionic acid (0.520 mL, 5.97 mmol) at room temperature. After 30 min, the reaction mixture was extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue, which was dissolved in THF (10 mL). To the solution was added $(Boc)_2O$ (500 mg, 2.38 mmol) and the mixture was stirred for 4 h under reflux. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:10) gave the title compound **14a** (175 mg, 44% yield) as colorless crystals: mp 84−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 9H), 2.71 (dd, J = 14.0, 9.8 Hz, 1H), 3.14 (dd, J = 14.9, 2.9 Hz, 1H), 3.82 (s, 3H), 4.59 (br, 2H), 7.19−7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 33.9, 53.3, 53.6, 80.1, 114.1, 126.6, 128.2, 128.9, 135.4, 154.4, 163.2. Anal. Calcd for $C_{16}H_{21}F_2NO_4$: C, 58.35; H, 6.43; N, 4.25. Found: C, 58.10; H, 6.36; N, 4.28.

Ethyl (2*E*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4,4-difluoro-6-phenylhex-2- enoate (15a). To a solution of the ester **14a** (685 mg, 2.08 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of DIBAL-H in toluene (1.0 M, 4.1 mL, 4.16 mmol) at −78 °C under argon, and the mixture was

stirred for 30 min at −78 °C. The reaction was quenched with saturated citric acid and extracted with Et_2O. The extract was washed with saturated citric acid and brine and dried over $MgSO_4$. Concentration under reduced pressure gave an oily aldehyde, which was used immediately in the next step without further purification. To a stirred suspension of LiCl (123 mg, 2.91 mmol) in MeCN (6 mL) under argon were added $(EtO)_2P(O)CH_2CO_2Et$ (0.577 mL, 2.91 mmol) and $(i\text{-}Pr)_2NEt$ (0.506 mL, 2.91 mmol) at 0 °C. After 20 min, the above aldehyde in MeCN (6 mL) was added to the mixture at 0 °C, and the mixture was stirred at room temperature for 4 h. The mixture was extracted with Et_2O, and the extract was washed with 0.5 N HCl and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:6) gave the title compound **15a** (515 mg, 67% yield) as colorless crystals: mp 93−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H), 2.67 (t, J = 12.6 Hz, 1H), 3.18 (dd, J = 14.5, 3.8 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 4.34 (br, 1H), 4.51 (d, J = 9.3 Hz, 1H), 6.33 (d, J = 15.9 Hz, 1H), 6.85 (dt, J = 15.6, 11.9 Hz, 1H), 7.18−7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 28.0, 34.2, 55.1, 61.0, 80.0, 119.3, 126.1, 126.5, 128.2, 128.8, 135.9, 137.0, 154.6, 164.3. Anal. Calcd for $C_{19}H_{25}F_2NO_4$: C, 61.78; H, 6.82; N, 3.79. Found: C, 61.85; H, 6.93; N, 3.78.

General Procedure for the Preparation of Organocopper Reagent (Me_2CuLi·LiCN·2LiCl·2LiBr) and Reduction of γ,γ-Difluoro-α,β-enoate: Synthesis of Ethyl (3*Z*)-5-[(*tert*-Butyl)dimethylsiloxy]-4-fluoro-6-phenylhex-3-enoate (16a) (Table 1, entry 1). To a solution LiCl (44 mg, 1.04 mmol) and CuCN (46 mg, 0.520 mmol) in THF (0.5 mL) was added a soluion of MeLi·LiBr in Et_2O (1.5 M, 0.693 mL, 1.04 mmol) at −78 °C under argon with additional stirring for 10 min. The mixture was allowed to warm to 0 °C and then stirred for 10 min at this temperature. To the recooled solution of the organocopper reagent to −78 °C was added a solution of the enoate **10a** (50 mg, 0.130 mmol) in THF (1 mL) under argon. The reaction was continued for 10 min and then quenched at 0 °C by addition of saturated NH_4Cl−28% NH_4OH solution (1:1) with additional stirring at room temperature for 30 min. The mixture was extracted with Et_2O, and the extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:20) gave a mixture of **16a** and **17a** (31 mg, 69% combined yield, **16a**:**17a** = 59:10).

Compound **16a**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.29 (s, 3H), −0.09 (s, 3H), 0.82 (s, 9H), 1.25 (t, J = 7.0 Hz, 3H), 2.79 (dd, J = 13.3, 8.4 Hz, 1H), 2.98 (dd, J = 13.4, 4.2 Hz, 1H), 3.12 (t, J = 7.8 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 4.22 (m, 1H), 5.01 (dt, J = 36.4, 7.3 Hz, 1H), 7.16−7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −5.0, 14.3, 18.2, 25.9, 29.4, 42.1, 60.8, 72.3, 98.2, 128.2, 129.7, 137.7, 159.8, 170.8; HRMS (FAB), *m*/*z* calcd for $C_{20}H_{32}FO_3Si$ (MH^+) 367.2105, found 367.2084.

Compound **17a**: colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 3.52 (d, J = 8.6 Hz, 2H), 4.52 (q, J = 7.0 Hz, 2H), 5.67 (dt, J = 19.2, 8.5 Hz, 1H), 6.20 (d, J = 15.7 Hz, 1H), 7.16−7.32 (m, 5H), 7.44 (d, J = 15.7 Hz, 1H).

Essentially same procedure was used in experiments in Table 1, entry 2 and in Table 2, entries 1 and 2.

General Procedure for the Preparation of 0.1 M SmI_2 in THF and Reduction of γ,γ-Difluoro-α,β-enoate (Table 1, entry 4). To a suspension of Sm powder (240 mg, 1.60 mmol) in THF (4 mL) was added a solution of CH_2I_2 (0.064 mL, 0.800 mmol) in THF (4 mL) at room temperature under argon. The mixture was stirred for 1 h. To a solution of the enoate **10a** (40 mg, 0.104 mmol) in THF−EtOH (3:1, 2 mL) was added the above solution of SmI_2 in THF (0.1 M, 6.2 mL, 0.624 mmol) at 0 °C under argon. After 1 h, the reaction mixture was quenched with saturated NH_4Cl and extracted with Et_2O. The extract was washed with saturated NH_4Cl and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:20) gave 35 mg (92% yield) of the mixture of the enoate **16a** and the ester **18a**. The product ratio was determined by ^{1}H NMR analysis (**16a**:**18a** = 73:27).

Compound **18a**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.55 (s, 3H), −0.09 (s, 3H), 0.77 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H), 2.12−2.48 (m, 2H), 2.55−2.65 (m, 3H), 2.91−3.02 (m, 1H), 3.96−4.05 (m, 1H), 4.16 (q, J = 7.2 Hz, 2H), 7.16−7.29 (m, 5H); HRMS (FAB), *m*/*z* calcd for $C_{20}H_{33}F_2O_3Si$ (MH^+) 387.2167, found 387.2171.

A procedure similar to that described above was used in experiments in Table 1, entry 5. Similar SmI_2-mediated reductions with *t*-BuOH as the proton source were applied to experiments in Table 1, entries 6−9. For the SmI_2−*t*-BuOH reduction protocol, see the following section.

Ethyl (3*Z*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4-fluoro-6-phenylhex-3-enoate (23a) (Table 2, entry 3). To a solution of the enoate **15a** (40 mg, 0.108 mmol) in THF−*t*-BuOH (3:1, 2 mL) was added a solution of SmI_2 in THF (0.1 M, 6.5 mL, 0.649 mmol) at 0 °C under argon. After 1 h, the reaction mixture was quenched with saturated NH_4Cl and extracted with Et_2O. The extract was washed with saturated NH_4Cl and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:7) gave the title compound **23a** (36 mg, 92% yield) as colorless crystals: mp 60−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H), 1.39 (s, 9H), 2.86−2.96 (m, 2H), 3.01−3.15 (m, 2H), 4.11 (q, J = 7.1 Hz, 2H), 4.49 (br, 1H), 4.68 (br, 1H), 4.87 (dt, J = 36.4, 7.2 Hz, 1H), 7.16−7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 28.2, 29.3, 38.5, 52.4, 60.7, 79.7, 99.1, 126.4, 128.1, 129.0, 136.1, 154.3, 158.2, 170.4. Anal. Calcd for $C_{19}H_{26}FNO_4$: C, 64.94; H, 7.46; N, 3.99. Found: C, 64.69; H, 7.40; N, 3.77.

Ethyl (3*S*)-2,2-Difluoro-3-{*N*-[(1*R*)-(2-methoxy-1-phenylethyl)]amino}-4- methylpentanoate (27). A solution of the aldehyde **24** (144 mg, 2.00 mmol) and the amine **25** (320 mg, 2.06 mmol) in THF (5 mL) was stirred at 0 °C for 4 h under argon in the presence of activated molecular sieves 3Å. To the mixture were successively added a suspension of Wilkinson's catalyst (92 mg, 0.100 mmol) in THF (6 mL), $BrCF_2CO_2Et$ (0.281 mL, 2.20 mmol), and a solution of Et_2Zn in hexane (1.0 M, 8.0 mL, 8.00 mmol). After being stirred for 30 min at 0 °C, the reaction was quenched with saturated $NaHCO_3$. The mixture was filtered over Celite and the filtrate was extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:10) gave the title compound **27** (333 mg, 50% yield) as a colorless oil: $[\alpha]^{23}_D$ −56.1 (*c* 0.93, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.84 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.63−1.80 (m, 1H), 2.92 (ddd, J = 15.6, 12.6, 2.9 Hz, 1H), 3.35 (dd, J = 9.9, 4.3 Hz, 1H), 3.38 (s, 3H), 3.47 (t, J = 9.1 Hz, 1H), 4.28−4.36 (m, 1H), 4.30 (q, J = 7.1 Hz, 2H), 7.23−7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 16.2, 21.1, 58.6, 59.9, 60.3, 62.7, 77.9, 118.0, 127.6, 128.1, 128.2, 139.9, 164.2; HRMS (FAB), *m*/*z* calcd for $C_{17}H_{26}F_2NO_3$ (MH^+) 330.1881, found 330.1874.

Ethyl (3*S*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-2,2-difluoro-4- methylpentanoate (28). To a solution of the ester **27** (820 mg, 2.49 mmol) in EtOH (10 mL) was added 20% palladium hydroxide on carbon (500 mg), and the suspension was stirred for 4 h under H_2 at room temperature. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give a colorless oil, which was dissolved in THF (10 mL). To the solution was added $(Boc)_2O$ (1.09 g, 4.98 mmol) and the mixture was stirred for 6 h under reflux. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:10) gave the title compound **28** (500 mg, 68% yield) as a colorless oil: $[\alpha]^{23}_D$ −10.9 (*c* 1.01, $CHCl_3$); ^{1}H NMR (270

MHz, $CDCl_3$) δ 0.95 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.5 Hz, 3H), 1.34 (t, J = 7.0 Hz, 3H), 1.43 (s, 9H), 2.02−2.19 (m, 1H), 4.10−4.25 (m, 1H), 4.31 (q, J = 6.7 Hz, 2H), 4.69 (d, J = 10.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 17.3, 22.8, 28.3, 56.5, 63.1, 80.1, 115.1, 155.2, 163.3; HRMS (FAB), *m*/*z* calcd for $C_{13}H_{24}F_2NO_4$ (MH^+) 296.1673, found 296.1678.

Ethyl (5*S*,2*E*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4,4-difluoro-6-methylhept-2-enoate (29). By use of a procedure similar to that described for the preparation of the enoate **15a**, the ester **28** (290 mg, 0.982 mmol) was converted into the title compound **29** (260 mg, 82% yield) as colorless crystals: mp 43−44 °C; $[\alpha]^{24}_D$ −5.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 3H), 100 (d, J = 6.9 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.44 (s, 9H), 2.08−2.22 (m, 1H), 3.85−4.04 (m, 1H), 4.23 (q, J = 7.0 Hz, 2H), 4.67 (d, J = 10.6 Hz, 1H), 6.30 (d, J = 15.8 Hz, 1H), 6.82 (dt, J = 15.8, 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 17.0, 22.8, 28.3, 58.2, 61.1, 80.1, 120.0, 122.5, 137.9, 155.5, 164.6. Anal. Calcd for $C_{15}H_{25}F_2NO_4$: C, 56.06; H, 7.84; N, 4.36. Found: C, 55.86; H, 7.74; N, 4.35.

Ethyl (5*S*,3*Z*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4-fluoro-6-methylhept-3- enoate (30). By use of a procedure similar to that described for SmI_2-mediated reduction of γ,γ-difluoro-α,β-enoate **15a** (Table 2, entry 3), the enoate **29** (50 mg, 0.156 mmol) was converted into the title compound **30** (40 mg, 85% yield) as a colorless oil: $[\alpha]^{21}_D$ −30.5 (*c* 1.02, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (d, J = 2.0 Hz, 3H), 0.96 (d, J = 2.0 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.45 (s, 9H), 1.83−1.98 (m, 1H), 3.09−3.17 (m, 2H), 3.90−4.07 (m, 1H), 4.14 (q, J = 7.0 Hz, 2H), 4.72 (d, J = 9.2 Hz, 1H), 4.98 (dt, J = 36.6, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 18.3, 19.4, 21.1, 28.3, 29.4, 57.3, 60.4, 79.7, 99.2, 155.0, 158.8, 170.8; HRMS (FAB), *m*/*z* calcd for $C_{15}H_{27}FNO_4$ (MH^+) 304.1924, found 304.1935.

Ethyl (5*R*,3*Z*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4-fluoro-6-phenylhex-3- enoate (35): colorless crystals; mp 60−61 °C; $[\alpha]^{20}_D$ −8.8 (*c* 0.80, $CHCl_3$); ^{1}H NMR and ^{13}C NMR same as compound **23a**. Anal. Calcd for $C_{19}H_{26}FNO_4$: C, 64.94; H, 7.46; N, 3.99. Found: C, 64.69; H, 7.40; N, 3.77.

***N*-[(1*R*)-1-Phenylethyl]-(5*S*,2*E*)-5-[*N*-(*tert*-butoxycarbonyl)amino]-4,4-difluoro-6-methylhept-2-enamide (31).** To a solution of the enoate **29** (100 mg, 0.311 mmol) in THF (0.4 mL) was added 1 N LiOH (0.342 mL, 0.342 mmol) at room temperature. The mixture was stirred for 1 h and extracted with EtOAc after acidification with 1 N HCl. The extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue, which was dissolved in THF (2 mL). To the solution were added (*R*)-methylbenzylamine (0.044 mL, 0.342 mmol), $(i\text{-Pr})_2$NEt (0.059 mL, 0.342 mmol), 1-hydroxybenzotriazole (52 mg, 0.342 mmol), and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (0.059 mL, 0.342 mmol) at room temperature. The mixture was stirred overnight and extracted with EtOAc. The extract was washed with saturated citric acid, saturated $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration under reduced pressure gave solid materials. Recrystallization of the solid from EtOAc−*n*-hexane gave the title compound **31** (60 mg, 48% yield) as colorless crystals: mp 188−190 °C; $[\alpha]^{14}_D$ +13.3 (*c* 0.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.41 (s, 9H), 1.54 (s, 3H), 2.08−2.19 (m, 1H), 3.88−4.00 (m, 1H), 4.67 (d, J = 11.0 Hz, 1H), 5.16−5.24 (m, 1H), 5.91 (d, J = 7.3 Hz, 1H), 6.28 (d, J = 15.6 Hz, 1H), 6.74 (dt, J = 15.1, 11.5 Hz, 1H), 7.25−7.38 (m, 5H); HRMS (FAB), *m*/*z* calcd for $C_{21}H_{31}F_2N_2O_3$ (MH^+) 397.2303, found 397.2292.

Ethyl (5*R*,3*Z*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4-fluoro-2-(1-hydroxy-1-methylethyl)-6-phenylhex-3-enoate (43) (Table 3, entry 2). To a mixture containing the enoate **34** (40 mg, 0.106 mmol) and acetone (0.024 mL, 0.324 mmol) in THF (1.5 mL) was added a solution of SmI_2 in THF (0.1 M, 3.2 mL, 0.324 mmol) at 0 °C under argon. After 1 h, the reaction mixture was quenched with saturated NH_4Cl and extracted with Et_2O. The extract was washed with saturated NH_4Cl and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:3) gave 37 mg (82%) of a mixture of diastereomers of the title compound **43** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 1.5H), 1.10 (s, 3H), 1.21 (s, 1.5H), 1.25 (t, J = 7.2 Hz, 1.5H), 1.27 (t, J = 7.1 Hz, 1.5H), 1.40 (s, 4.5H), 1.41 (s, 4.5H), 2.86−3.02 (m, 1H), 3.42 (d, J = 7.1 Hz, 0.5 H), 3.44 (d, J = 7.1 Hz, 0.5H), 4.07−4.22 (m, 2H), 4.50 (br, 1H), 4.69 (br, 1H), 4.86 (dd, J = 35.6, 10.4 Hz, 0.5H), 4.89 (dd, J = 35.6, 10.4 Hz, 0.5H), 7.14−7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 26.2, 26.4, 28.2, 38.3, 50.5, 52.9, 60.9, 71.4, 79.9, 102.0, 128.1, 128.2, 129.0, 136.0, 154.2, 161.6, 171.6; HRMS (FAB), *m*/*z* calcd for $C_{22}H_{33}FNO_5$ (MH^+) 410.2343, found 410.2353.

Ethyl (5*R*,3*Z*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-2-ethoxycarbonyl-4-fluoro-6- phenylhex-3-enoate (44) (Table 3, entry 3). To a mixture containing the enoate **34** (80 mg, 0.217 mmol) and $(EtOCO)_2O$ (0.157 mL, 1.09 mmol) in THF (2.0 mL) was added a solution of SmI_2 in THF (0.1 M, 13.0 mL, 1.30 mmol) at 0 °C under argon. After 1 h, the reaction mixture was quenched with saturated NH_4Cl and extracted with Et_2O. The extract was washed with saturated NH_4Cl and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:6) gave the title compound **44** (70 mg, 76% yield) as a colorless oil: $[\alpha]^{20}_D$ −8.2 (*c* 0.86, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 6.6 Hz, 3H), 1.39 (s, 9H), 2.95 (d, J = 5.9 Hz, 2H), 4.11−4.23 (m, 4H), 4.40 (d, J = 9.6 Hz, 1H), 4.55 (br, 1H), 4.68 (d, J = 8.9 Hz, 1H), 5.07 (dd, J = 35.3, 9.6 Hz, 1H), 7.14−7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 28.4, 38.5, 47.8, 52.3, 61.8, 61.9, 80.0, 99.4, 126.7, 128.3, 129.2, 135.9, 154.4, 159.7, 166.9, 167.1; HRMS (FAB), *m*/*z* calcd for $C_{22}H_{31}FNO_6$ (MH^+) 424.2135, found 424.2141.

Ethyl (5*R*,3*Z*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4-fluoro-2-hydroxymethyl- 6-phenylhex-3-enoate (45) (Table 3, entry 4). To a solution of 2,6-diphenylphenol (800 mg, 3.25 mmol) in CH_2Cl_2 (8 mL) was added a solution of Me_3Al in *n*-hexane (1.02 M, 1.59 mL, 1.62 mmol) at room temperature under argon. After 1 h, a solution of *s*-trioxane (48 mg, 0.541 mmol) in CH_2Cl_2 (2 mL) was added to the reaction mixture at 0 °C. After 1 h, to the reaction mixture were successively added a solution of the enoate **34** (100 mg, 0.271 mmol) in THF (2 mL) and a solution of SmI_2 in THF (0.1 M, 8.1 mL, 0.812 mmol) at 0 °C. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with saturated NH_4Cl and extracted in the usual manner. Purification by flash chromatography over silica gel with EtOAc−*n*-hexane (1:2) gave the title compound (mixture of diastereomer) **45** (67 mg, 65% yield) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 1.5H), 1.25 (t, J = 7.1 Hz, 1.5H), 1.40 (s, 4.5H), 1.42 (s, 4.5H), 2.86−3.00 (m, 2H), 3.52−3.63 (m, 2H), 3.65−3.68 (m, 0.5H), 3.71−3.76 (m, 0.5H), 4.08−4.20 (m, 2H), 4.46 (br, 1H), 4.63−4.76 (br, 1H), 4.70 (dd, J = 37.0, 9.3 Hz, 0.5H), 4.76 (dd, J = 36.4, 9.6 Hz, 0.5H), 7.17 (d, J = 7.2 Hz, 2H), 7.21−7.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 28.2, 38.4, 43.4, 53.0, 61.0, 63.0, 79.9, 101.6, 126.6, 128.1, 128.2, 135.8, 153.8, 157.3, 171.9; HRMS (FAB), *m*/*z* calcd for $C_{20}H_{29}FNO_5$ (MH^+) 382.2030, found 382.2023.

(2*S*)-2-{(3*R*,1*Z*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-2-fluoro-4-phenylbut-1-enyl}propano-3-lactone (47) and Its (2*R*)-Diastereomer (48). To a solution of the enoate **45** (63 mg, 0.189 mmol) in THF (0.2 mL) was added 1 N LiOH (0.182 mL, 0.182 mmol) at room temperature. After 3 h, the reaction mixture was acidified with 1 N HCl and extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure gave the oily carboxylic acid **46**. To a solution of Ph_3P (43 mg, 0.167 mmol) and **46** in THF (0.5 mL) was added a solution of DEAD in toluene (40%, 0.075 mL, 0.167 mmol) at −78 °C under argon. After 10 min of stirring at −78 °C, a solution of the above carboxylic acid in THF (1 mL) was added to the mixture at

−78 °C. After 2 h, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography over silica gel with EtOAc−*n*-hexane (1:3) to give the title compound **47** and its diastereomer **48** (total 19 mg, 37% yield, **47**:**48** = 1:1).

Compound **47**: colorless crystals; mp 82−84 °C; $[\alpha]^{13}_D$ −9.3 (*c* 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.95 (d, J = 6.8 Hz, 2H), 4.05 (t, J = 5.0 Hz, 1H), 4.43 (t, J = 6.0 Hz, 1H), 4.44 (br, 1H), 4.54 (br, 1H), 4.68 (br, 1H), 4.84 (dd, J = 35.2, 8.6 Hz, 1H), 7.13−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 38.5, 47.6, 52.7, 65.0, 80.3, 98.6, 126.9, 128.4, 129.2, 135.7, 154.4, 160.6, 168.4. Anal. Calcd for $C_{18}H_{22}FNO_4$: C, 64.46; H, 6.61; N, 4.18. Found: C, 64.18; H, 6.72; N, 4.04.

Compound **48**: colorless crystals; mp 107−110 °C; $[\alpha]^{25}_D$ +97.7 (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.95 (d, J = 6.6 Hz, 2H), 3.95 (t, J = 4.9 Hz, 1H), 4.41 (dd, J = 6.8, 5.1 Hz, 1H), 4.50 (br, 1H), 4.56−4.62 (m, 1H), 4.64 (br, 1H), 4.82 (dd, J = 34.9, 8.8 Hz, 1H), 7.14−7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 38.3, 47.4, 52.5, 65.0, 80.3, 98.5, 126.9, 128.5, 129.2, 135.7, 154.4, 160.7, 168.5. Anal. Calcd for $C_{18}H_{22}FNO_4$: C, 64.46; H, 6.61; N, 4.18. Found: C, 64.43; H, 6.78; N, 3.96.

Methyl (2*R*,5*R*,3*Z*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4-fluoro-2-(2-methylpropyl)-6-phenylhex-3-enoate (49). To a mixture consisting of β-lactone **47** (18 mg, 0.0537 mmol) and CuBr·Me_2S (3.3 mg, 0.0161 mmol) in THF−Me_2S (0.840 mL, 20:1) was added dropwise a solution of *i*-PrMgCl in Et_2O (0.32 mL, 0.32 mmol) at −23 °C under argon. After being stirred for 1 h at −23 °C, the reaction mixture was quenched with 1 N HCl and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give an oil. To a solution of the above oil in MeOH−benzene (0.3 mL, 1:2) was added $TMSCHN_2$ in hexane (2.0 M, 0.080 mL, 0.161 mmol) at room temperature. After 3 h, the reaction mixture was quenched with AcOH and extracted with EtOAc. The extract was washed with 5% $NaHCO_3$ and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:8) gave the title compound **49** (9 mg, 40% yield) as a colorless oil: $[\alpha]^{25}_D$ −17.5 (*c* 0.46, $CHCl_3$); $\Delta\epsilon$ = −2.34 (214 nm, isooctane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 6.6 Hz, 6H), 1.26−1.54 (m, 3H), 1.40 (s, 9H), 2.92 (d, J = 7.1 Hz, 2H), 3.50 (br, 1H), 3.60 (s, 3H), 4.45 (br, 1H), 4.63 (dd, J = 36.3, 10.1 Hz, 1H), 4.65 (br, 1H), 7.13−7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 22.8, 25.7, 28.4, 38.5, 39.0, 41.5, 51.9, 52.8, 79.9, 105.6, 126.6, 128.2, 129.2, 136.2, 154.5, 157.8, 173.9; HRMS (FAB), *m*/*z* calcd for $C_{22}H_{33}FNO_4$ (MH^+) 394.2393, found 394.2403.

Methyl (2*S*,5*R*,3*Z*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4-fluoro-2-(2-methylpropyl)-6-phenylhex-3-enoate (51). By use of a procedure similar to that described for the preparation of the ester **49**, the β-lactone **48** (18 mg, 0.0537 mmol) was converted into the title compound **51** (14 mg, 66% yield) as a colorless oil: $[\alpha]^{23}_D$ +33.4 (*c* 0.69, $CHCl_3$); $\Delta\epsilon$ = +3.01 (217 nm, isooctane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, J = 5.6 Hz, 6H), 1.15−1.30 (m, 3H), 1.41 (s, 9H), 2.88 (dd, J = 13.7, 8.1 Hz, 1H), 2.95 (br, 1H), 3.43−3.51 (m, 1H), 3.64 (s, 3H), 4.46 (br, 1H), 4.60 (dd, J = 36.2, 10.1 Hz, 1H), 4.70 (br, 1H), 7.13−7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 22.8, 25.3, 28.4, 38.4, 38.7, 41.3, 51.7, 52.8, 79.8, 105.5, 126.4, 128.1, 129.1, 136.1, 154.3, 157.3, 173.8; HRMS (FAB), *m*/*z* calcd for $C_{22}H_{33}FNO_4$ (MH^+) 394.2393, found 394.2387.

Methyl (2*R*,5*R*,3*Z*)-2-Benzylsulfanylmethyl-5-[*N*-(*tert*-butoxycarbonyl)amino]-4-fluoro-6-phenylhex-3-enoate (50). To a solution of β-lactone **47** (5 mg, 0.0149 mmol) in DMF (0.2 mL) was added benzylmercaptan (0.010 mL, 0.0596 mmol) at room temperature. After 60 h at room temperature, the reaction mixture was extracted with EtOAc and the extract was washed with 1 N HCl and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give an oil. To a solution of the above oil in MeOH−benzene (0.1 mL, 1:2) was added $TMSCHN_2$ in hexane (2.0 M, 0.022 mL, 0.0447 mmol) at room temperature. After 3 h, the reaction mixture was quenched with AcOH and extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:6) gave the title compound **50** (2.8 mg, 39% yield) as a colorless oil: $[\alpha]^{23}_D$ +10.9 (*c* 0.09, $CHCl_3$); $\Delta\epsilon$ = −2.69 (209 nm, isooctane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 2.45 (q, J = 6.7 Hz, 1H), 2.67 (dd, J = 13.2, 8.3 Hz, 1H), 2.92 (d, J = 6.8 Hz, 2H), 3.55−3.76 (m, 3H), 3.64 (s, 3H), 4.47 (br, 1H), 4.62 (br, 1H), 4.64 (dd, J = 35.4, 10.0 Hz, 1H), 4.68 (br, 1H), 7.10−7.32 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.6, 32.9, 36.1, 38.3, 41.0, 51.2, 52.4, 79.8, 103.5, 126.5, 126.8, 128.1, 128.2, 128.6, 129.1, 135.5, 137.5, 153.8, 161.1, 172.0; HRMS (FAB), *m*/*z* calcd for $C_{26}H_{33}FNO_4S$ (MH^+) 474.2114, found 474.2109.

Methyl (2*S*,5*R*,3*Z*)-2-Benzylsulfanylmethyl-5-[*N*-(*tert*-butoxycarbonyl)amino]-4-fluoro-6-phenylhex-3-enoate (52). By use of a procedure similar to that described for the preparation of the ester **50**, the β-lactone **48** (5 mg, 0.0149 mmol) was converted into the title compound **52** (2.6 mg, 37% yield) as a colorless oil: $[\alpha]^{25}_D$ +68.5 (*c* 0.15, $CHCl_3$); $\Delta\epsilon$ = +1.31 (217 nm, isooctane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.33 (dd, J = 13.4, 6.1 Hz, 1H), 2.52−2.61 (m, 1H), 2.87−2.94 (m, 2H), 3.59−3.70 (m, 3H), 3.68 (s, 3H), 4.45 (br, 1H), 4.64 (dd, J = 35.5, 9.9 Hz, 1H), 4.68 (br, 1H), 6.99−7.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.6, 31.9, 36.1, 38.5, 41.5, 52.0, 52.4, 79.9, 103.6, 126.6, 126.8, 128.1, 128.2, 128.6, 129.1, 135.5, 137.5, 154.0, 161.1, 172.0; HRMS (FAB), *m*/*z* calcd for $C_{26}H_{33}FNO_4S$ (MH^+) 474.2114, found 474.2121.

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Supporting Information Available: Experimental procedure for compounds in the b-series of Schemes 1 and 2; ORTEP diagrams for **31** and **36** and their CIF files; copies of ^{1}H NMR spectra of compounds **16a**, **16b**, **23a**, **23b**, **30**, and **47**−**52**; cand opies of CD spectra of compounds **49**−**52**. This material is available free of charge via the Internet at http://pubs.acs.org.

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