A Stereocontrolled Synthesis of Monofluoro Ketomethylene Dipeptide Isosteres

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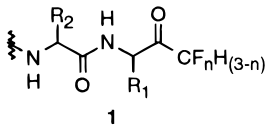
A simple, stereocontrolled synthesis of monofluoro ketomethylene dipeptide isosteres has been developed. N-Tritylated ketomethylene dipeptide isosteres, prepared from N-tritylated amino acids, are converted to their Z-TMS enol ethers and fluorinated with Selectfluor. There is cooperative stereocontrol between the *N*-tritylamine group and the alkyl group at C-2. The method is short (six steps), diastereoselective (85 → 95%), and enantioselective (>95%).

Introduction

The incorporation of fluorine into biologically active molecules can induce unique changes in the physical, chemical, and biological properties of that compound.[1] Fluorinated peptide mimetics are particularly interesting in this regard.[2] They contain fluorine-activated electrophilic carbonyl groups that react readily with active site nucleophiles such as hydroxyl groups (serine proteases), thiol groups (cysteine proteases), or water (aspartate or metallo proteinases) to produce transition-state analogues in the active site.[3]

Many examples utilize fluorinated *methyl* ketones **1** ($n = 3$, 2) to provide the electrophilic carbonyl group.[3−5] Monofluoromethyl ketone analogues **1** ($n = 1$) have the interesting tendency to exhibit both reversible and irreversible inhibition.[3c,6] Because the fluorinated methyl ketone functionality in **1** defines the carboxyl end of the chain, the peptide chain can only be extended in the P direction. A second design used a fluorinated α-ketoester **2** to provide the electrophilic carbonyl group.[7] In this case, the peptide chain can only be extended in the P′-direction.



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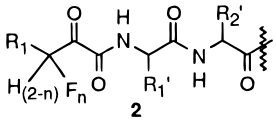

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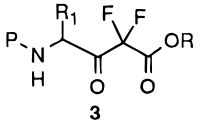

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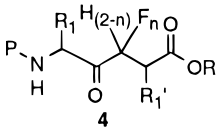

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Incorporating α-fluorinated ketones *within* the peptide chain is less common. Difluorostatone analogues **3** have been studied as difluorinated dipeptide mimetics.[8] Few examples of true difluoroketomethylene dipeptide isosteres **4** ($n = 2$) are extant,[9] and only a single example of a monofluoroketomethylene dipeptide isostere **4** ($n = 1$) has been reported.[10] Monofluoroketomethylene peptide isosteres **4** ($n = 1$) could be very interesting peptide mimetics since they are true peptide isosteres whose binding region can be extended in both the P and P′ directions. Moreover, the ketone carbonyl group is only partially hydrated (∼0−50%) upon treatment with water so that interaction with several different types of proteases is possible.

The first synthesis of a monofluoro ketomethylene peptide isostere **5** utilized a homoenolate equivalent to assemble the isostere skeleton and fluorination of a silyl enol ether to introduce the C-3 fluorine substituent.[10] Overall, this route was long (>10 steps), and the introduction of fluorine was completely nonstereoselective. On the basis of our chiral alkylation methodology for the synthesis of ketomethylene peptide isosteres,[11] our use of the trityl group as a powerful stereocontrol element

(1) Hudlicky, M., Pavlath, A. E., Eds. *Chemistry of Organic Fluorine Compounds II*; ACS Monograph 187; American Chemical Society: Washington, DC, 1995. See the following chapters: Filler, R.; Kirk, K. Biological Properties of Fluorinated Compounds; Elliott, A. J. Fluorinated Pharmaceuticals; Lang, R. W. Fluorinated Agrochemicals.

(2) (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons: New York, 1991. (b) Rich, D. H. In *Comprehensive Medicinal Chemistry*; Sammes, P. G., Ed.; Pergamon Press: Oxford, U.K. 1990; pp 391−441. (c) Sham, H. L. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington D.C., 1996; pp 184−195.

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(4) See, for example: (a) Reference 3d. (b) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Smith, S. A.; Petrillo, E. W., Jr. *J. Med. Chem.* **1993**, *36*, 2431. (b) Edwards, P. D.; Andisik, D. W.; Strimpler, A. M.; Gomes, B.; Tuthill, P. A. *J. Med. Chem.* **1996**, *39*, 1112 and references therein.

(5) Perfluoroethyl ketones have also been reported: Angelastro, M. R.; Burkhart, J. P.; Bey, P.; Peet, N. P. *Tetrahedron Lett.* **1992**, *33*, 3265 and references therein.

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(8) (a) Veerapandian, B.; Cooper, J. B.; Sali, A.; Bllundell, T. L.; Rosati, R. L.; Dominy, B. W.; Damon, D. B.; Hoover, D. J. *Protein Sci.* **1992**, *1*, 322. (b) James, M. N. G.; Sielecki, A. R.; Hayakawa, K.; Gelb, M. H. *Biochemistry* **1992**, *31*, 3872. (c) Beveridge, A. J.; Dealwis, C.; Cooper, J. B. *THEOCHEM* **1995**, *333*, 87 and references therein. (d) Jones, D. M.; Atrash, B.; Tegernilsson, A. C.; Gyzander, E.; Deinum, J.; Szelke, M. *Lett. Peptide Sci.* **1995**, *2*, 147.

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(11) Hoffman, R. V.; Tao, J.-H. *Tetrahedron* **1997**, *53*, 7119.

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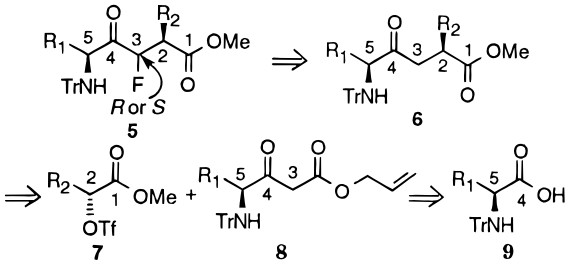
Scheme 1



in the synthesis of sphingosines,[12] and the use of Selectfluor ((1-chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate)) for electrophilic fluorination of silyl enol ethers,[13] we envisioned the simple and stereoselective synthesis of monofluoroketomethylene peptide isosteres **5** shown retrosynthetically in Scheme 1. While the conversion of tritylated amino acids **9** to ketomethylene peptide isosteres **6** could follow a known route,[11] the stereoselective fluorination of **6** to monofluoro isostere **5** depended on the unprecedented allylic stereocontrol by an N-trityl group and/or 1,2 stereocontrol by the R-group at C-2. (It was claimed in the earlier report that *no* stereocontrol of the fluorination was observed.[10]) A preliminary report demonstrated that this approach is feasible.[13b] The successful reduction of Scheme 1 to practice and the factors that control the fluorination stereochemistry is the subject of this report.

Results and Discussion

Tritylated amino acids **9**[14] containing branched, unbranched, and heteroatom-containing side chains were converted to allyl β-ketoesters **8**[15] (55−75%), alkylated with scalemic triflates **7**,[11] and decarboxylated to provide tritylated ketomethylene isosteres **6**[16] in good yields (40−60%) (Scheme 2). In our previous work, a *tert*-butyl ester group was used in the β-ketoester **8**.[11] Since TFA removal of the *tert*-butyl group is incompatible with the trityl group, allyl esters were utilized instead. Palladium(0) not only cleaved the allyl group selectively but also catalyzed the decarboxylation to give **6**.[12]

The (*R*)-enantiomer of triflate **7** produces the *R* configuration at C-2 of **6**, which has the same stereochemical sense as a normal dipeptide. The *S* enantiomer of **7** gives the unnatural stereochemical analogue at C-2. The diastereoselectivity of the alkylation−decarboxylation was quite good, ranging from 85 to 95% de (Table 1). In each case, the major diastereomer of **6** was separated and examined using the chiral shift reagent Eu(hfc)$_3$.

Within the limits of NMR detection, only one enantiomer was present (>95% ee), indicating that no epimerization at C-5 takes place during the reaction sequence.[17]

syn-(2*R*,5*S*)-Isosteres **6aa**, **6ab**, **6bc**, **6cd**, **6de**, and **6ea**[16] were converted to the corresponding (*Z*)-TMS enol ethers **10** using NaHMDS−TMSCl (Scheme 3). It is known that bulky nitrogen substituents on amino ketones cause enolate formation to occur regiospecifically distal from the amino group by removal of the α′-proton.[12,18] Moreover, only one vinyl proton signal was seen in the olefin region of the NMR spectra of **10**, indicating a single double-bond geometry was produced. The use of NaHMDS under kinetic conditions[19] allows the *Z* geometry to be assigned to **10**.

Scheme 2

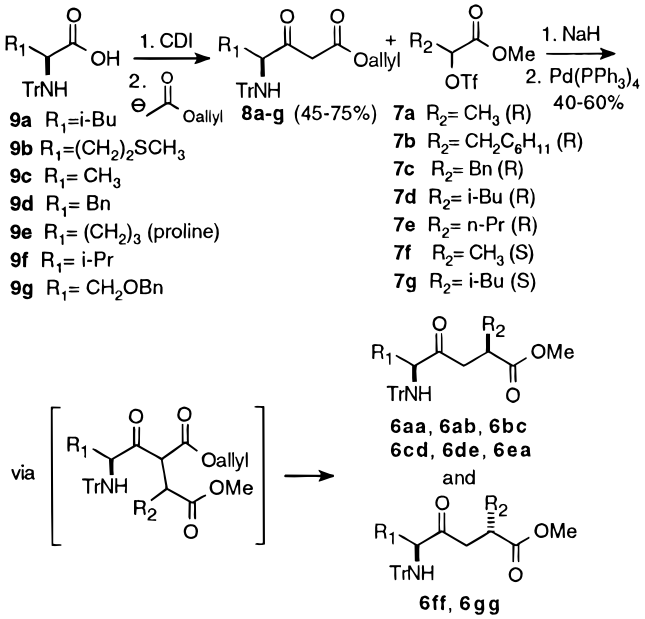
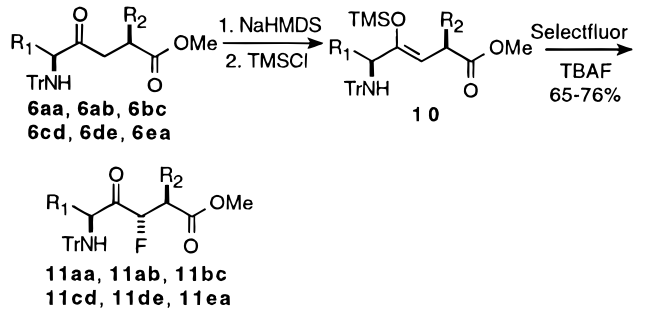


Table 1. Yields and Stereochemical Purities of Isosteres 6

entry	product	yield[a] (%)	de[b] (%)	ee[c] (%)
1	**6aa**	60	>95	>95
2	**6ab**	49	85	>95
3	**6bc**	43	91	>95
4	**6cd**	50	92	>95
5	**6de**	53	92	>95
6	**6ea**	40	85	>95
7	**6ff**	55	>95	>95
8	**6gg**	50	90	>95

[a] Isolated yields of chromatographed mixtures of diastereomers. [b] Determined by ^{1}H NMR for the mixture of diastereomers. [c] Determined by chiral LIS study using Eu(hfc)$_3$ on the separated major diastereomer.

Scheme 3



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(13) (a) Hoffman, R. V.; Saenz, J. E. *Tetrahedron Lett.* **1997**, *38*, 8469. (b) Hoffman, R. V.; Tao. J. *Tetrahedron Lett.*, in press. (c) Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, 1.

(14) Barlos, K.; Papaioannou, D.; Theodoropoulos, D. *J. Org. Chem.* **1982**, *47*, 1324.

(15) Harris, B. D.; Joullie, M. M. *Tetrahedron* **1988**, *44*, 3489.

(16) For the combinations used, the reaction of ketoester **8x** (derived from amino acid **9x**) with triflate **7y** gives γ-ketoester **6xy**.

(17) For calibrating the LIS method to determine enantioselectivity, racemic **7aa** was prepared and subjected to examination by the LIS reagent.

(18) (a) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1988**, *110*, 7447. (b) Alexander, C. W.; Liotta, D. C. *Tetrahedron Lett.* **1996**, *37*, 1961 and references therein.

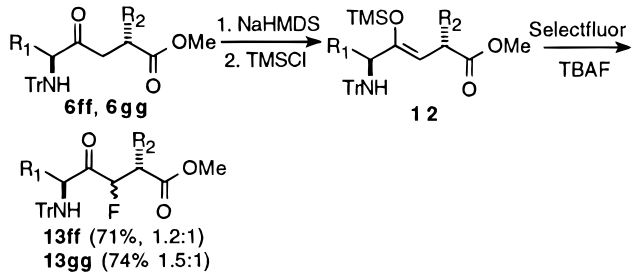
(19) (a) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (b) Xie, L.; Isenberger, K. M.; Held, G.; Dahl, L. M. *J. Org. Chem.* **1997**, *62*, 7516.

Table 2. Stereochemical Results of the Preparation of Monofluoro Ketomethylene Dipeptide Isosteres 9

entry	product	yield[a] (%)	de[b] (%)
1	**9aa**	76	>95
2	**9ab**	73	>95
3	**9bc**	65	>95
4	**9cd**	75	>95
5	**9de**	68	>95
6	**9ea**	~15	>95
7	**9ff**	71	1.2:1
8	**9gg**	74	1.5:1

[a] Isolated yields of chromatographed mixtures of diastereomers. [b] Determined by ^{1}H NMR of the mixture of diastereomers.

Scheme 4

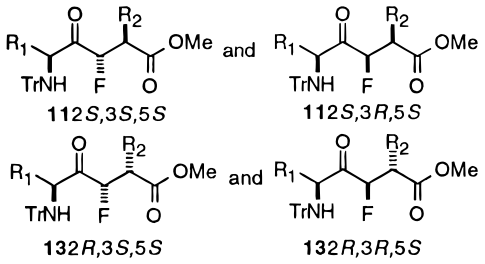


Direct fluorination of either **10aa** or **10ab** with Selectfluor in DMF or MeCN was very sluggish, the major process being cleavage of the trityl group. In contrast, treatment of **10** with Selectfluor in the presence of TBAF led to smooth α′-fluorination to produce monofluoro ketomethylene dipeptide isosters **11** in generally good yields (65−76%) (Scheme 3). Proline derivative **10ea** gave a low yield (15%) presumably due to steric hindrance. It is noteworthy that the methionine derivative **10bc** also gave a good yield since it is known that sulfides can be oxidized by Selectfluor under similar conditions.[20] Even more noteworthy is that *only a single diastereomer was evident in the NMR spectrum of the monofluorinated products* **11**. Thus, the *N*-tritylamino group and/or the C-alkyl group (or both) exert significant stereocontrol in the electrophilic fluorination of **10** (Table 2).

When *anti*-(2*S*,5*S*)-isosteres **6ff** and **6gg** were converted to (*Z*)-TMS enol ethers **12** and fluorinated by the same protocol, mixtures of diastereomers **13** were produced (Scheme 4, Table 2). Since the configuration at C-5 remained the same, this result suggests that there is a cooperative effect of the *N*-tritylamino group and the C-2 alkyl group in determining the stereoselectivity of fluorination.

The NMR signal of the C-3 proton was used to assign the stereochemistry of the products. The fluorination of **10** produced single diastereomers of **11** whose C-3 proton signal appeared at δ ~4.4−4.9 with J_{H-H} = 7−8 Hz. The major diastereomer produced by the fluorination of **12** also had δ ~4.4−4.6 and J_{H-H} = 7.8−8.7 Hz. The minor diastereomer formed in the fluorination of **12** had the same chemical shift for C-3 proton but had J_{H-H} = 4.6−4.8 Hz.

The two possible diastereomers of **11** are shown below. Since the absolute configurations at C-2 and C-5 are known, only the configuration of the fluorine atom at C-3 is variable.[21] Using $R_1 = R_2 = CH_3$ for calculational simplicity, conformations about the 2−3, 3−4, and 4−5 bonds were evaluated by the AM-1 method.[22] For **11***S*,*S*,*S* there were three low energy conformations that were 1.7−3.0 kcal/mol more stable than the next lowest energy conformer, and they all had a dihedral angle of 179.5° between the C-2 and C-3 protons. For **11***S*,*R*,*S* the conformation of lowest energy was also 2.5 kcal more stable than the next lowest energy conformation, but it had a dihedral angle of only 83.2° between the C-2 and C-3 protons. The substantial coupling constant of J_{H-H} = 7−8 Hz found in the product is consistent the 179.5° dihedral angle found for the major conformers of the **11***S*,*S*,*S* diastereomer. (Similar calculational results were found for R_1 = *i*-Pr, R_2 = Me.)



The same conformational analysis was carried out on the diastereomers of **13**. Again, each diastereomer was found to have one conformation preferred by about 2.5 kcal/mol over the next lowest ones. The most stable conformer of **13***R*,*R*,*S* was found to have a dihedral angle between the C-2 and C-3 protons of 170°, and the most stable conformer of **13***R*,*S*,*S* was found to have a dihedral angle of 77° between these protons. Thus, the major isomer, which has J_{H-H} = 7.8−8.7 Hz, can be assigned as the **13***R*,*R*,*S* isomer, and the minor diastereomer, which has J_{H-H} = 4.6−4.8 Hz, can be assigned as the **13***R*,*S*,*S* isomer.

From these results, it is seen that for the *syn*-2*R*,5*S* isomers of **6** (i.e., **6aa**, **ab**, **bc**, **cd**, **de**, **ea**) the chiralities at C-2 and C-5 are complementary in dictating the *S*-configuration at C-3, and thus, high diastereoselectivity is observed. In the *anti*-2*S*,5*S* diastereomers of **6** (i.e., **6ff** and **6gg**), the 1,3-allylic stereocontrol afforded by the *N*-tritylamine group is opposed by the 1,2 stereocontrol of the chiral center at C-2, and diastereomeric mixtures are obtained.

Conformational analysis of the TMS-enol ethers **10** and **12** provides an explanation for this stereoselection, at least in a simplistic manner (Figure 1). Again using R_1, R_2 = Me for calculational simplicity, the preferred conformation of **10**, which lies 3 kcal/mol lower than the next lowest energy conformer, minimizes $A_{1,2}$ interactions and has both the *N*-trityl group at C-5 and the methyl group at C-2 above one face of the enol double bond. Approach of the fluorinating agent from the face opposite these groups leads to the observed stereochemistry.

The preferred conformation of **12**, which also lies 3 kcal/mol below the next lowest conformer, has the *N*-trityl group at C-5 and the methyl group at C-2 on opposite faces of the double bond (Figure 1). The 1,2 stereocontrol of the methyl group must be comparable to 1,3-allylic

(20) Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791.

(21) This is based on the very reasonable assumption that epimerization at C-2 or C-5 does not occur during the fluorination.

(22) The semiempirical AM1 calculations were performed on a Silicon Graphics workstation (Indigo 2) using the MOPAC program in Insight II (4.0.0) from MSI. The input geometries for the AM1 calculations were obtained by using the Discover force field (Steepest first 1000 steps and then Newton; Derivative = 0.001) within Insight II (4.0.0).

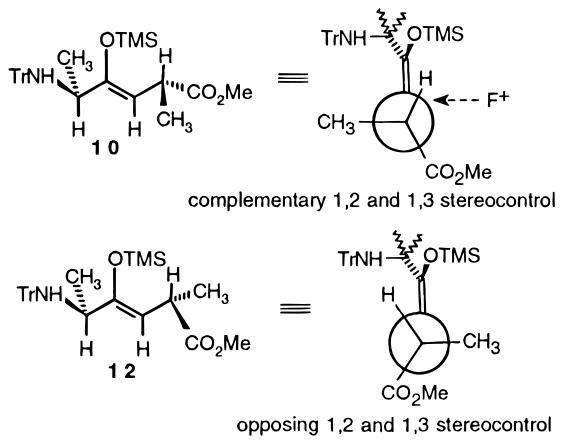
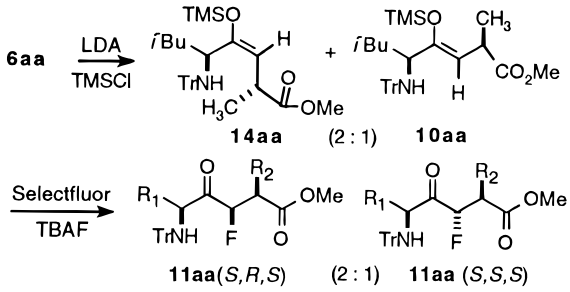


Figure 1.

Scheme 5

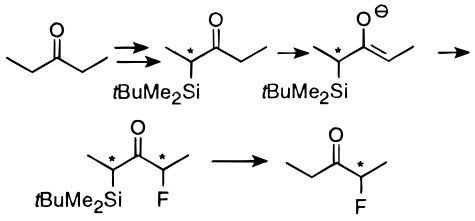


stereocontrol by the *N*-trityl group, and a mixture of diastereomers is produced. This rationale is consistent with the observation that replacement of the C-2 methyl group of **12ff** with a slightly larger C-2 isobutyl group in **12gg** leads to an increase in the diastereoselectivity as well (Scheme 4). More work is needed to confirm the validity of these models, but they do provide a paradigm for understanding the stereocontrol that is observed.

On the basis of the stereoselectivity observed in the fluorination of the (*Z*)-enol ether **10**, we thought it might be possible to reverse the diastereoselectivity by using the corresponding (*E*)-enol ether **14** as the fluorination substrate. Thus, **6aa** was converted to the (*E*)-TMS enol ether **14aa** by using LDA as the base (Scheme 5).[19] Two isomeric TMS enol ethers were produced in a 2:1 ratio. The minor isomer was the (*Z*)-TMS enol ether **10aa** as indicated by its vinyl proton signal. The major isomer was assigned as **14aa**. Apparently, the bulk of the C-5 carbon and the secondary C-2 carbon make formation of the (*E*)-enolate difficult; thus, an *E*,*Z*-mixture is produced under conditions that normally give predominantly the (*E*)-enolate.[19]

Fluorination of this mixture gave a 2:1 mixture of monofluoro ketomethylene peptide isosteres. The major diastereomer had the C-3 proton signal at δ 4.61 with $J_{H-H} = 5.4$ Hz. The reduced coupling constant is consistent with **11aa**(*S*,*R*,*S*) as described above. The minor diastereomer had $J_{H-H} = 7$ Hz for the C-3 proton signal at δ 4.84 and was thus **11aa**(*S*,*S*,*S*), which comes from the diastereospecific fluorination of **10aa** in the mixture. Since the fluorination of **10aa** was shown to be stereospecific (see above), and since the ratio of fluorinated diastereomeric products (2:1) is the same as the ratio of (*E*)- and (*Z*)-enol ethers **14aa** and **10aa**, it is reasonable to conclude that the fluorination of (*E*)-enol ether **14aa** is also diastereospecific. The stereochemical reversal at

Scheme 6



C-3 shows the that same facial bias by the fluorinating agent toward the double bond is operative; the problem in diastereoselection lies in forming the (*E*)-enolate cleanly in these very bulky aminoketones.

Asymmetric synthesis of α-fluoroketones has been the object of several recent studies.[23] In general, asymmetric fluorinating agents derived from camphor are used to fluorinate ketone enolates.[24] This approach, however, generally gives modest enantioselectivity (<75% ee). Enders recently described the electrophilic fluorination of chiral α-silyl ketone enolates.[23] In this case, the α-silyl group provides stereocontrol for fluorination at the α′-position and is subsequently removed (Scheme 6). High de's are found for cyclic ketones. Lower de's (67−89%) are found for acyclic ketones, but both enantiomers can be produced by choosing either the (*Z*)- or (*E*)-enolate geometry.

The present work has similar elements in that a bulky *N*-trityl group exerts stereocontrol from the α′- position and the stereochemistry can be varied by choice of enol geometry. The results have also allowed a working model to be generated to rationalize the stereoselection. However, the complex functional and chiral environment found in the densely functionalized substrates employed requires further work to fully understand the structural factors that control diastereoselection.

In summary, a simple, stereocontrolled synthesis of monofluoro ketomethylene dipeptide isosteres has been developed. The method is short (six steps), diastereoselective (85 → 95%), and enantioselective (>95%).

Experimental Section

Infrared spectra were recorded either on neat liquids or KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, in $CDCl_3$. Thin-layer chromatography was performed on silica gel 60 F_{254} plates from EM reagents and visualized by UV irridiation and/or iodine. Analytical HPLC was performed with the indicated solvent systems and flow rates on 8 mm × 25 mm cm silica gel columns using UV detection. Preparative thin-layer chromatography was performed on silica gel 60 F_{254} plates from EM reagents and visualized by UV irradiation. Flash chromatography was performed using silica gel 60 (230−400 mesh). Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Tetrahydrofuran was distilled from benzophenone ketyl. Other solvents were HPLC grade and were used without further purification. Starting materials were purchased from Aldrich, Sigma, or Novabiochem and used as received. Elemental analyses were carried out by M-H-W laboratories, Phoenix, AZ.

Allyl 4-Tritylamino-3-oxo-6-methylheptanoate, 8a. General Procedure. To a stirred solution of *N*-tritylleucine (1.05 g, 2.81 mmol) in THF (20 mL) was added CDI (carbonyl

(23) For an excellent literature survey, see: Enders, D.; Potthoff, M.; Raabe, G.; Runsink, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2362.
(24) For a nucleophilic alternative, see: Kabat, M. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1417.

diimidazole, 503 mg, 2.81 mmol) at room temperature under a N_2 atmosphere. The resulting solution was stirred for 5 h at the same temperature and used for the next reaction without further purification. Meanwhile, a solution of lithium *tert*-butoxycarbonylmethanide was made from BuLi (2.50 M, 3.54 mL, 8.85 mmol), diisopropylamine (1.63 mL, 8.85 mmol), and allyl acetate (0.69 mL, 6.40 mmol). The above imidazole solution was added dropwise to this pale yellow solution of lithium enloate at −78 °C under a N_2 atmosphere. The resulting mixture was warmed to room temperature 60 min, quenched with H_2O (50 mL), and extracted with ether (3 × 50 mL). The organic extracts were combined, washed with brine 100 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide **8a** as a a colorless oil: yield 71% after purification by flash chromatography (hexane/ether = 75:20); $[\alpha]^{25}_D$ +37.4 (*c* 1.04, $CHCl_3$); ^{1}H NMR(keto form) δ 0.83 (d, 3H, J = 7.0 Hz), 0.86 (d, 3H, J = 6.8 Hz), 1.28 (m, 1H), 1.44 (m, 1H), 1.74 (m, 1H), 2.85 (d, 1H, J = 16.1 Hz), 3.02 (d, 1H, J = 16.1 Hz), 3.47 (m, 1H), 4.52 (d, 2H, J = 5.6 Hz), 5.22 (m, 2H), 5.81 (m, 1H), 7.21−7.46 (two set of m, 15H); ^{13}C NMR δ 22.6, 23.3, 24.5, 43.7, 45.6, 61.3, 65.5, 71.4, 89.6, 118.4, 126.7, 128.0, 129.0, 131.8, 146.0, 166.7, 205.9; FTIR (neat) 2947, 1745, 1177, 1148, 918, 734 cm^{-1}. Anal. Calcd for $C_{30}H_{33}O_3N$: C, 79.09; H, 7.30; N, 3.07. Found: C, 78.98; H, 7.23; N, 3.13.

Allyl 4-tritylamino-3-oxo-6-S-methylhexanoate, 8b: 50% of a colorless oil after purification by flash chromatography (hexane/ether = 85:10); $[\alpha]^{25}_D$ +78.8 (*c* 0.914, $CHCl_3$); ^{1}H NMR δ 1.28 (m, 1H), 1.90 (m, 1H), 2.07 (s, 3H), 2.43 (m, 1H), 2.62 (d, 1H, J = 16.1 Hz), 3.08 (d, 1H, J = 16.1 Hz), 3.66 (m, 1H), 4.52 (m, 2H), 5.23 (m, 2H), 5.81 (m, 1H), 7.24−7.55 (m, 15H); ^{13}C NMR δ 15.6, 29.4, 33.1, 45.2, 61.5, 65.7, 71.4, 118.6, 126.8, 128.0, 128.9, 132.2, 146.1, 166.3, 177.5, 204.8; FTIR (neat) 2937, 1745, 1716, 709 cm^{-1}. Anal. Calcd for $C_{29}H_{31}O_3NS$: C, 73.54; H, 6.60; N, 2.96. Found: C, 73.36; H, 6.45; N, 2.89.

Allyl 4-tritylamino-3-oxo-pentanoate, 8c: 70% of a colorless oil after purification by flash chromatography (hexane/ether = 85:10); $[\alpha]^{25}_D$ +40.8 (*c* 0.897, $CHCl_3$); ^{1}H NMR δ 1.25 (d, 6H, J = 7.0 Hz), 2.66 (d, 1H, J = 16.1 Hz), 2.96 (d, 1H, J = 16.1 Hz), 3.06 (d, 1H, J = 8.6 Hz), 3.50 (m, 1H), 4.50 (m, 2H), 5.30 (m, 2H), 5.75 (m, 1H), 7.21−7.46 (m, 15H); ^{13}C NMR δ 20.0, 45.7, 58.2, 65.6, 71.4, 118.5, 127.2, 128.5, 129.3, 132.1, 146.7, 166.9, 206.7; FTIR (neat) 2967, 1745, 1716, 709 cm^{-1}. Anal. Calcd for $C_{27}H_{27}O_3N\cdot 0.5H_2O$: C, 76.75; H, 6.68; N, 3.32. Found: C, 77.15; H, 6.30; N, 2.97.

Allyl 4-tritylamino-3-oxo-5-phenylpentanoate, 8d: 70% of a colorless oil after purification by flash chromatography (hexane/ether = 75:20); $[\alpha]^{25}_D$ +53.7 (*c* 0.659, $CHCl_3$); ^{1}H NMR (keto form) δ 2.49 (d, 1H, J = 16.3 Hz), 2.61 (d, 1H, J = 16.3 Hz), 2.87 (m, 2H), 3.70 (m, 1H), 4.48 (m, 2H), 5.21 (m, 2H), 5.79 (m, 1H), 7.31 (m, 20H); ^{13}C NMR (mixture of keto and enol) δ 39.8, 45.9, 62.9, 64.6, 70.4, 117.7, 125.8, 127.1, 127.7, 128.2, 128.8, 129.2, 129.9, 130.9, 136.0, 143.7, 145.2, 163.8, 165.6, 204.8; FTIR (neat) 3057, 1750, 1715, 1492, 1158, 704 cm^{-1}. Anal. Calcd for $C_{33}H_{31}O_3N$: C, 80.95; H, 6.38; N, 2.86. Found: C, 80.76; H, 6.46; N, 2.76.

Allyl 4-[(*N*-trityl)pyrrolidine-2]-3-oxo-propanoate, 8e: 45% of a colorless oil after purification by flash chromatography (hexane/ether = 85:10); $[\alpha]^{25}_D$ −33.1 (*c* 2.31, $CHCl_3$); ^{1}H NMR δ 1.17−1.45 (set of m, 4H), 2.93 (m, 2H), 3.43 (d, 1H, J = 15.5 Hz), 3.72 (d, 1H, J = 15.5 Hz), 4.08 (dd, 1H, J = 2.9, 9.5 Hz), 4.63 (m, 2H), 5.30 (m, 2H), 5.85 (m, 1H), 7.19−7.53 (m, 15H); ^{13}C NMR δ 24.2, 29.7, 46.2, 50.8, 65.8, 69.5, 87.7, 118.6, 126.3, 127.8, 129.2, 131.8, 144.8, 167.0, 206.1; FTIR 2947, 1745, 1716, 709 cm^{-1}. Anal. Calcd for $C_{29}H_{29}O_3N$: C, 79.24; H, 6.65; N, 3.19. Found: C, 79.22; H, 6.44; N, 3.03.

Allyl 4-tritylamino-3-oxo-5-methylhexanoate, 8f: 64% of a colorless oil after purification by flash chromatography (hexane/ether = 85:10); $[\alpha]^{25}_D$ +67.9 (*c* 2.36, $CHCl_3$); ^{1}H NMR δ 0.93 (d, 3H, J = 7.0 Hz), 1.10 (d, 3H, J = 7.0 Hz), 2.10 (m, 1H), 2.40 (d, 1H, J = 16.5 Hz), 3.00 (d, 1H, J = 16.5 Hz), 3.04 (d, 1H, J = 9.8 Hz), 3.45 (dd, 1H, J = 3.7, 9.8 Hz), 4.50 (m, 2H), 5.20 (m, 2H), 5.79 (m, 1H), 7.21−7.46 (m, 15H); ^{13}C NMR δ 18.9, 19.5, 32.5, 48.1, 65.8, 66.6, 71.4, 118.7, 127.0, 128.3, 129.5, 132.2, 146.8, 166.9, 205.5; FTIR (neat) 2967, 1745, 1716, 709 cm^{-1}. Anal. Calcd for $C_{29}H_{31}O_3N$: C, 78.88; H, 7.08; N, 3.17. Found: C, 78.63; H, 6.84; N, 2.96.

Allyl 4-tritylamino-3-oxo-5-benzyloxypentanoate, 8g: 74% of a white solid, which was obtained by trituration. After concentration, the yellow residue was dissolved in hexanes (100 mL) and filtered, and the solid was washed with cold Et_2O (50 mL): mp 106−108 °C; $[\alpha]^{25}_D$ +45.0 (*c* 1.29, $CHCl_3$); ^{1}H NMR δ 2.75 (d, 1H, J = 16.6 Hz), 3.11 (m, 2H), 3.43 (d, 1H, J = 16.6 Hz), 3.69 (m, 2H), 4.38 (s, 2H), 4.51 (d, 2H, J = 5.6 Hz), 5.22 (m, 2H), 5.82 (m, 1H), 7.21−7.41 (m, 20H); ^{13}C NMR δ 47.9, 61.8, 65.5, 72.5, 73.0, 73.4, 118.2, 126.7, 128.0, 128.8, 132.0, 146.0, 166.6, 206.4; FTIR (neat) 3027, 1750, 1720, 1452, 1098, 749, 709 cm^{-1}. Anal. Calcd for $C_{34}H_{33}O_4N$: C, 78.59; H, 6.40; N, 2.70. Found: C, 78.70; H, 6.36; N, 2.86.

(2*R*,5*S*)-Trityl-LeuΨ[COCH$_2$]Ala-OMe, 6aa. General Procedure. A solution of 3-oxo ester **8a** (940 mg, 2.27 mmol) in THF (10 mL) was added dropwise to a stirred suspension of NaH (101 mg of 60% in oil, 2.52 mmol) in dry THF (30 mL) at 0 °C under nitrogen. The mixture was stirred for 10 min. Then a solution of triflate **7a** (590 mg, 2.50 mmol) in dichloromethane (10 mL) was added dropwise to this gray suspension of the 3-oxo ester enolate. The resulting mixture was stirred at room temperature for 36 h, quenched with cold citric acid (5%, 50 mL), and extracted with ether (2 × 100 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide a pale yellow oil. Without further purification, the above oil was dissolved into THF (18 mL) under nitrogen and treated with $Pd(PPh_3)_4$ (264 mg, 0.232 mmol) followed by morpholine (2.02 mL, 23.2 mmol). After 3 h, the solvent was evaporated, and the residue was taken into ether (100 mL) and filtered. The filtrate was washed with 5% citric acid (50 mL), H_2O (20 mL), dried ($MgSO_4$), and passed through a short pad of silica gel to afford a white solid **6aa** (623 mg, 1.36 mmol, 60%) after purification by flash chromatography (hexane/ether = 85:5): de >95% based on ^{1}H NMR of the crude; ee >95% by a chiral LIS study using $Eu(hfc)_3$ in comparison with a racemic sample; mp 114.5−116.5 °C; $[\alpha]^{25}_D$ +73.2 (*c* 0.343, $CHCl_3$); ^{1}H NMR δ 0.90 (d, 3H, J = 6.2 Hz), 0.93 (d, 6H, J = 6.6 Hz), 1.44 (m, 3H), 1.83 (m, 1H), 2.40 (m, 1H), 2.55 (m, 2H), 3.00 (br, 1H), 3.41 (m, 1H), 3.58 (s, 3H), 7.24−7.44 (two set of m, 15H); ^{13}C NMR δ 17.2, 22.9, 23.4, 24.5, 33.9, 44.1, 44.7, 51.7, 59.6, 71.2, 126.4, 127.7, 129.1, 146.6, 176.4, 212.2; FTIR (neat) 2927, 1735, 1720 cm^{-1}. Anal. Calcd for $C_{30}H_{35}O_3N$: C, 78.78; H, 7.71; N, 3.06. Found: C, 78.60; H, 7.53; N, 2.98.

(2*R*,5*S*)-Trityl-LeuΨ[COCH$_2$]Cha-OMe, 6ab: yield 49% of a colorless oil after purification by flash chromatography (hexane/ether = 85:5); de 85% based on ^{1}H NMR; the major diastereomer had ee >95%; $[\alpha]^{25}_D$ +29.1 (*c* 2.39, $CHCl_3$); ^{1}H NMR δ 0.80 (d, 3H, J = 6.6 Hz), 0.84 (d, 3H, J = 8.8 Hz), 1.11−1.75 (set of m, 16H), 2.14 (d, 2H, J = 6.8 Hz), 2.55 (m, 1H), 2.73 (br, 1H), 3.38 (m, 1H), 3.61 (s, 3H), 7.20−7.39 (two set of m, 15H); ^{13}C NMR δ 22.9, 23.9, 24.9, 26.5, 33.2, 33.8, 35.7, 37.4, 40.2, 41.7, 44.7, 51.8, 61.2, 71.8, 127.0, 128.3, 129.5, 146.6, 176.8, 212.5; FTIR (neat) 2927, 1735, 1720, 709 cm^{-1}. Anal. Calcd for $C_{36}H_{45}O_3N\cdot H_2O$: C, 77.52; H, 8.49; N, 2.51. Found: C, 77.53; H, 8.24; N, 2.30.

(2*R*,5*S*)-Trityl-MetΨ[COCH$_2$]Phe-OMe, 6bc: yield 43% of a white solid after purification by flash chromatography (hexane/ether = 85:5); de 91% based on ^{1}H NMR; the major diastereomer had ee >95%; mp 120−121 °C; $[\alpha]^{25}_D$ +70.0 (*c* 2.56, $CHCl_3$); ^{1}H NMR δ 1.99 (m, 2H), 2.11 (s, 3H), 2.29−2.53 (set of m, 5H), 2.80 (m, 2H), 3.12 (d, 1H, J = 9.6 Hz), 3.50 (m, 1H), 3.56 (s, 3H), 7.05−7.41 (two set of m, 20H); ^{13}C NMR δ 15.4, 29.2, 33.6, 37.8, 41.0, 41.4, 51.6, 59.9, 71.2, 16.4, 127.8, 128.5, 128.8, 138.3, 146.2, 174.9, 210.1; FTIR (neat) 2947, 1735, 1716, 709 cm^{-1}. Anal. Calcd for $C_{35}H_{37}O_3NS$: C, 76.19; H, 6.76; N, 2.54. Found: C, 76.05; H, 6.68; N, 2.52.

(2*R*,5*S*)-Trityl-AlaΨ[COCH$_2$]Leu-OMe, 6cd: yield 50% of a colorless oil after purification by flash chromatography (hexane/ether = 85:5); de 90% based on ^{1}H NMR; the major diastereomer had ee >95%; $[\alpha]^{25}_D$ +40.0 (*c* 1.33, $CHCl_3$); ^{1}H NMR δ 0.80 (d, 3H, J = 10.6 Hz), 0.83 (d, 3H, J = 10.7 Hz), 0.95 (m, 2H), 1.16 (d, 3H, J = 7.0 Hz), 1.32 (m, 1H), 1.93 (dd,

1H, J = 6.6, 17.9 Hz), 2.17 (dd, 1H, J = 6.6, 17.9 Hz), 2.53 (m, 1H), 3.42 (m, 1H), 3.60 (s, 3H), 7.20−7.44 (two set o m, 15H); ^{13}C NMR δ 19.3, 20.8, 21.7, 24.9, 25.5, 36.7, 40.2, 56.8, 70.3, 125.4, 127.9, 28.8, 145.2, 175.0, 211.0; FTIR (neat) 2957, 1735, 1720, 709 cm^{-1}. Anal. Calcd for $C_{30}H_{35}O_3N\cdot0.5H_2O$: C, 77.22; H, 7.78; N, 3.01. Found: C, 77.78; H, 7.36; N, 2.56.

(2*R*,5*S*)-Trityl-PheΨ[COCH$_2$]Nva-OMe, 6de: yield 53% of a colorless oil after purification by flash chromatography (hexane/ether = 85:10); de 92% based on ^{1}H NMR; the major diastereomer had ee >95%; $[\alpha]^{25}_D$ +52.2 (*c* 1.15, $CHCl_3$); ^{1}H NMR δ 0.77 (t, 3H, J = 6.2 Hz), 1.04 (m, 4H), 1.68 (m, 2H), 2.25 (m, 1H), 2.77 (m, 2H), 3.60 (s, 3H), 3.56 (m, 1H), 7.17−7.33 (m, 20H); ^{13}C NMR δ 13.8, 20.1, 34.1, 39.0, 41.7, 43.0, 51.4, 63.5, 71.2, 126.6, 127.9, 128.0, 129.6, 146.2, 175.8, 212.2; FTIR (neat) 2957, 1735, 1720, 709 cm^{-1}. Anal. Calcd for $C_{35}H_{37}O_3N$: C, 80.89; H, 7.18; N, 2.70. Found: C, 81.07; H, 7.15; N, 2.60.

(2*R*,5*S*)-Trityl-ProΨ[COCH$_2$]Ala-OMe, 6ea: yield 40% of a colorless oil after purification by flash chromatography (hexane/ether = 85:10); de 85% based on ^{1}H NMR; the major diastereomer had ee >95%; $[\alpha]^{25}_D$ −18.8 (*c* 0.554, $CHCl_3$); ^{1}H NMR δ 0.84−1.43 (set of m, 4H), 1.18 (d, 3H, J = 6.8 Hz), 2.04 (m, 2H), 2.87−3.05 (two set of m, 3H), 3.34 (m, 1H), 3.68 (s, 3H), 7.24−7.52 (two set of m, 15H); ^{13}C NMR δ 17.6, 24.6, 29.9, 34.5, 43.7, 50.8, 52.3, 69.0, 74.4, 126.6, 128.2, 128.7, 145.4, 176.8, 212.4; FTIR (neat) 2967, 1735, 1720, 714 cm^{-1}. Anal. Calcd for $C_{29}H_{31}O_3N\cdot0.5H_2O$: C, 77.30; H, 7.16; N, 3.11. Found: C, 77.05; H, 7.34; N, 3.32.

(2*S*,5*S*)-Trityl-ValΨ[COCH$_2$]Ala-OMe, 6ff: yield 55% of a colorless oil after purification by flash chromatography (hexane/ethyl acetate = 85:2.5); de > 95% based on ^{1}H NMR; the major diastereomer had ee >95%; $[\alpha]^{25}_D$ +159.1 (*c* 0.933, $CHCl_3$); ^{1}H NMR δ 0.90 (d, 3H, J = 6.5 Hz), 0.93 (d, 3H, J = 6.8 Hz), 1.06 (d, 3H, J = 6.9 Hz), 1.82 (dd, 1H, J = 4.0, 17.8 Hz), 2.02 (m, 1H), 2.18 (dd, 1H, J = 8.4, 17.8 Hz), 2.40 (m, 1H), 3.36 (m, 1H), 3.61 (s, 3H), 7.20−7.46 (two set of m, 15H); ^{13}C NMR δ 15.7, 17.9, 31.4, 32.9, 43.7, 50.5, 64.4, 69.9, 125.4, 126.7, 128.1, 145.5, 175.0, 209.4; FTIR (neat) 2967, 1735, 1716, 709 cm^{-1}. Anal. Calcd for $C_{29}H_{33}O_3N$: C, 78.52; H, 7.50; N, 3.16. Found: C, 78.75; H, 7.34; N, 3.05.

(2*S*,5*S*)-Trityl-Ser(OBn)Ψ[COCH$_2$]Leu-OMe, 6gg: yield 50% of a colorless oil after purification by flash chromatography (hexane/ethyl acetate = 85:15); de 90% based on ^{1}H NMR; the major diastereomer had ee >95%; $[\alpha]^{25}_D$ +60.5 (*c* 0.887, $CHCl_3$); ^{1}H NMR δ 0.76 (d, 6H, J = 6.2 Hz), 0.82 (d, 3H, J = 6.4 Hz), 0.95 (m, 2H), 1.33 (m, 1H), 1.92 (dd, 1H, J = 6.2, 17.9 Hz), 2.48 (dd, 1H, J = 6.2, 17.9 Hz), 2.59 (m, 1H), 3.20 (m, 1H), 3.57 (m, 2H), 3.62 (s, 1H), 4.38 (s, 2H), 7.20−7.44 (two set of m, 20H); ^{13}C NMR δ 20.8, 21.8, 24.9, 36.8, 40.2, 42.8, 50.4, 60.4, 70.0, 71.8, 72.4, 125.5, 126.8, 127.9, 145.2, 175.2, 210.8; FTIR (neat) 2957, 1735, 1716, 730 cm^{-1}. Anal. Calcd for $C_{37}H_{41}O_3N$: C, 78.83; H, 7.33; N, 2.48. Found: C, 78.73; H, 7.09; N, 2.45.

(2*S*,3*S*,5*S*)-Trityl-LeuΨ[COCFH]Ala-OMe, 11aa. General Procedure. At −78 °C, NaHMDS (2.0 M in THF, 0.27 mL, 0.54 mmol) was added to a solution of **6aa** (190 mg, 0.41 mmol) in THF (20 mL). After 3.5 h at the same temperature, TMSCl (0.1 mL, 0.51 mmol) in THF (10 mL) was added. The resulting solution was warmed to rt for 1 h and then taken up into hexanes (150 mL), washed with ice-cold saturated aqueous sodium bicarbonate (20 mL), dried (Na_2SO_4), filtered, and concentrated to provide a residue. The ^{1}H NMR of the yellow residue showed only one doublet in the vinyl region and one methoxy singlet. This indicated that only a single enol ether isomer was formed. Under nitrogen, the residue was suspended into DMF (3 mL), cooled to −50 °C, and treated with Selectfluor (150 mg, 0.42 mmol) in DMF (3 mL). After 15 min, the solution was reacted with TBAF ($(Bu)_4N^+F^-$) (1.0 M in THF, 0.42 mL, 0.42 mmol). The resulting mixture was warmed to rt for 45 min, treated with cold aqueous $NaHCO_3$ (0.5 M, 10 mL), extracted with ether (50 mL × 2), dried ($MgSO_4$), and concentrated to provide **11aa** as a colorless oil (157 mg, 0.33 mmol, 76%) and a second component shown to be diastereomerically pure starting material **6aa** (about 24%) after a careful separation by flash chromatography (hexane/ether = 85:2.5): de >95% based on ^{1}H NMR of the crude product; $[\alpha]^{25}_D$ +65.2 (*c* 0.940, $CHCl_3$); ^{1}H NMR δ 0.84 (d, 3H, J = 6.6 Hz), 0.90 (d, 3H, J = 6.5 Hz), 0.99 (d, 3H, J = 5.7 Hz), 1.43 (m, 2H), 1.78 (m, 1H), 2.42 (m, 1H), 2.97 (d, 1H, J = 8.0 Hz), 3.65 (s, 3H), 3.90 (m, 1H), 4.84 (dd, 1H, J = 6.9, 46.6 Hz), 7.46−7.51 (two set of m, 15H); ^{13}C NMR δ 11.7, 22.9, 23.3, 24.6, 40.2 (d, ^2J = 21.9 Hz), 43.4, 52.0, 71.2, 94.2 (d, ^1J = 187.7 Hz), 126.4, 127.8, 128.9, 146.2, 173.4, 209.5 (d, ^2J = 23.5 Hz); FTIR (neat) 2947, 1740, 1726, 709 cm^{-1}. Anal. Calcd for $C_{30}H_{34}O_3NF$: C, 75.76; H, 7.21; N, 2.95. Found: C, 75.60; H, 7.47; N, 2.76.

(2*S*,3*S*,5*S*)-Trityl-LeuΨ[COCFH]Cha-OMe, 11ab. The ^{1}H NMR of the intermediate TMS-enol ether shows only one doublet in the vinyl region and one methoxy singlet: yield 73% of a colorless oil together with about 27% recovered starting material after flash chromatography (hexane/ether = 85:2.5); de >95% based on ^{1}H NMR of the crude product; $[\alpha]^{25}_D$ +51.3 (*c* 2.52, $CHCl_3$); ^{1}H NMR δ 0.83 (d, 3H, J = 6.6 Hz), 0.87 (d, 3H, J = 6.5 Hz), 0.92−1.80 (set of m, 16H), 2.57 (m, 1H), 2.93 (br, 1H), 3.64 (s, 3H), 3.84 (m, 1H), 4.41 (dd, 1H, J = 7.7, 45.8 Hz), 7.26−7.49 (two set of m, 15H); ^{13}C NMR δ 23.0, 26.2, 32.5, 33.5, 35.4, 43.6, 44.8 (d, ^2J = 20.2 Hz), 51.8, 56.5, 59.3, 71.2, 93.7 (d, ^1J = 187.7 Hz), 126.6, 128.0, 129.0, 146.3, 172.6, 209.1 (d, ^2J = 24.6 Hz); FTIR (neat) 2927, 1740, 1726, 704 cm^{-1}. Anal. Calcd for $C_{36}H_{44}O_3NF\cdot0.5H_2O$: C, 75.99; H, 7.88; N, 2.36. Found: C, 76.29; H, 8.00; N, 2.47.

(2*S*,3*S*,5*S*)-Trityl-MetΨ[COCFH]Phe-OMe, 11bc. The ^{1}H NMR of the intermediate TMS-enol ether shows only one doublet in the vinyl region and one methoxy singlet: yield 65% of a white solid together with about 30% recovered starting material after flash chromatography (hexane/ethyl acetate = 85:2.5); de >95% based on ^{1}H NMR of the crude product; mp 124−126 °C; $[\alpha]^{25}_D$ +96.1 (*c* 1.68, $CHCl_3$); ^{1}H NMR δ 1.97−2.28 (m, 2H), 2.18 (s, 3H), 2.47 (m, 1H), 2.67−2.92 (m, 2H), 3.01−3.13 (m, 2H), 3.59 (s, 3H), 4.02 (m, 1H), 4.92 (dd, 1H, J = 9.0, 47.1 Hz), 7.08−7.42 (set of m, 20H); ^{13}C NMR δ 15.4, 28.8, 32.3, 33.2, 47.6 (d, ^2J = 14.6 Hz), 52.0, 56.7, 71.1, 92.1 (d, ^1J = 185.3 Hz), 126.4, 127.0, 127.7, 128.8, 137.5, 146.1, 170.8, 210.1 (d, ^2J = 21.0 Hz); FTIR (neat) 2967, 1740, 1726, 709 cm^{-1}. Anal. Calcd for $C_{35}H_{36}O_3NSF$: C, 73.79; H, 6.37; N, 2.46. Found: C, 73.64; H, 6.48; N, 2.35.

(2*S*,3*S*,5*S*)-Trityl-AlaΨ[COCFH]Leu-OMe, 11cd. The ^{1}H NMR of the intermediate TMS-enol ether shows only one doublet in the vinyl region and one methoxy singlet: yield 75% of a colorless oil together with about 25% recovered starting material after flash chromatography (hexane/ethyl acetate = 85:2.5); de >95% based on ^{1}H NMR of the crude product; $[\alpha]^{25}_D$ +39.6 (*c* 1.88, $CHCl_3$); ^{1}H NMR δ 0.84 (d, 6H, J = 4.8 Hz), 1.20 (d, 3H, J = 7.0 Hz), 1.11−1.56 (m, 3H), 2.51 (m, 1H), 3.06 (br, 1H), 3.64 (s, 3H), 3.90 (m, 1H), 4.54 (dd, 1H, J = 7.8, 46.0), 7.23−7.50 (two set of m, 15H); ^{13}C NMR δ 21.9, 25.0, 28.7, 30.1, 35.7, 44.4 (d, ^2J = 16.2 Hz), 50.7, 56.9, 70.2, 91.9 (d, ^1J = 189.3 Hz), 125.4, 126.0, 127.7, 145.2, 171.2, 208.8 (d, ^2J = 25.0 Hz); FTIR (neat) 2967, 1740, 1730, 704 cm^{-1}. Anal. Calcd for $C_{30}H_{34}O_3NF$: C, 75.76; H, 7.21; N, 2.95. Found: C, 75.61; H, 7.40; N, 2.76.

(2*S*,3*S*,5*S*)-Trityl-PheΨ[COCFH]Nva-OMe, 11de. The ^{1}H NMR of the intermediate TMS-enol ether shows only one doublet in the vinyl region and one methoxy singlet. Yield 68% of a colorless oil together with about 32% recovered starting material after flash chromatography (hexane/ethyl acetate = 85:2.5); de >95% based on ^{1}H NMR of the crude product; $[\alpha]^{25}_D$ +86.0 (*c* 3.36, $CHCl_3$); ^{1}H NMR δ 0.88 (t, 3H, J = 7.4 Hz), 1.23 (m, 2H), 1.52 (m, 2H), 2.44−2.74 (two set of m, 2H), 3.07 (m, 2H), 3.59 (s, 3H), 4.20 (m, 1H), 4.65 (dd, 1H, J = 8.9, 50.0 Hz), 7.11−7.40 (set of m, 20H); ^{13}C NMR δ 12.6, 19.1, 28.5, 38.1, 45.0 (d, ^2J = 19.4 Hz), 50.7, 58.2, 69.6, 92.7 (d, ^1J = 183.7 Hz), 125.3, 125.7, 126.7, 127.3, 128.0, 129.6, 137.2, 145.2, 170.7, 209.6 (d, ^2J = 26.7 Hz); FTIR (neat) 2957, 1740, 1726, 709 cm^{-1}. Anal. Calcd for $C_{35}H_{36}O_3NF\cdot0.5H_2O$: C, 76.90; H, 6.82; N, 2.56. Found: C, 76.52; H, 6.53; N, 2.48.

(2*R*,3*R*,5*S*)-Trityl-ValΨ[COCFH]Ala-OMe, 13ff. The ^{1}H NMR of the intermediate TMS-enol ether shows only one doublet in the vinyl region and one methoxy singlet: yield 71% of a colorless oil together with about 29% recovered starting

material after flash chromatography (hexane/ethyl acetate = 85:2.5); de 1.2:1.0 based on ^{1}H NMR of the crude product. The major diastereomer (2*R*,3*R*,5*S*) has the following characteristics: $[\alpha]^{25}_D$ +51.6 (*c* 1.23, $CHCl_3$); ^{1}H NMR δ 0.93 (d, 3H, *J* = 7.0 Hz), 1.00 (d, 3H, *J* = 7.3 Hz), 1.04 (d, 3H, *J* = 6.9 Hz), 1.94 (m, 1H), 2.40 (m, 1H), 3.68 (s, 3H), 4.04 (m, 1H), 4.58 (dd, 1H, *J* = 8.7, 46.0 Hz), 7.26−7.55 (two set of m, 15H); ^{13}C NMR δ 12.2, 16.2, 19.1, 31.0, 40.6 (d, ^2J = 19.4 Hz), 50.9, 61.5, 69.6, 93.1 (d, ^1J = 182.0 Hz), 125.4, 126.7, 128.1, 145.3, 171.8, 207.2 (d, ^2J = 27.4 Hz); FTIR (neat) 2967, 1740, 1726, 704 cm^{-1}. Anal. Calcd for $C_{29}H_{32}O_3NF$: C, 75.46; H, 6.99; N, 3.03. Found: C, 75.66; H, 7.17; N, 2.98. The minor (2*R*,3*S*,5*S*) diastereomer has the following characteristics: ^{1}H NMR δ 0.86 (d, 3H, *J* = 7.0 Hz), 0.97 (d, 3H, *J* = 6.6 Hz), 1.24 (d, 3H, *J* = 6.9 Hz), 1.96 (m, 1H), 2.71 (m, 1H), 3.66 (S, 3H), 3.95 (m, 1H), 3.96 (dd, 1H, *J* = 4.6, 46.3 Hz), 7.26−7.55 (two set of m, 15H); ^{13}C NMR δ 9.87, 14.8, 20.2, 28.5, 39.8 (d, ^2J = 21.0 Hz), 51.0, 59.9, 69.3, 93.8 (d, ^1J = 182.9 Hz), 125.4, 126.7, 128.2, 145.4, 171.7, 208.9 (d, ^2J = 26.3 Hz); FTIR (neat) 2967, 1740, 1726, 704 cm^{-1}.

(2*R*,3*R*,5*S*)-Trityl-Ser(OBn)Ψ[COCFH]Leu-OMe, 11gg. The ^{1}H NMR of the intermediate TMS-enol ether shows only one doublet in the vinyl region and one methoxy singlet: yield 74% of a colorless oil together with about 26% recovered starting material after flash chromatography (hexane/ethyl acetate = 85:5); de 1.8:1.0 based on ^{1}H NMR of the crude product. The major diastereomer (2*R*,3*R*,5*S*) has the following characteristics: $[\alpha]^{25}_D$ +46.1 (*c* 1.04, $CHCl_3$); ^{1}H NMR δ 0.84 (d, 6H, *J* = 5.9 Hz), 1.27−1.47 (m, 3H), 2.62 (m, 1H), 3.24 (m, 2H), 3.64 (s, 3H), 4.17 (m, 1H), 4.41 (d, 1H, *J* = 3.1 Hz), 4.44 (d, 1H, *J* = 3.1 Hz), 4.63 (dd, 1H, *J* = 7.8, 45.8 Hz), 7.25−7.49 (two set of m, 20H); ^{13}C NMR δ 20.6, 22.0, 25.0, 35.8, 44.3 (d, ^2J = 20.2 Hz), 50.7, 58.4, 69.9, 70.6, 72.1, 92.6 (d, ^1J = 186.3 Hz), 125.6, 127.0, 127.7, 136.8, 145.0, 171.3, 205.6 (d, ^2J = 27.4 Hz); FTIR (neat) 2957, 1735 (br), 704 cm^{-1}. Anal. Calcd for $C_{37}H_{40}O_4NF$: C, 76.39; H, 6.93; N, 2.41. Found: C, 76.19; H, 7.05; N, 2.42. The minor (2*R*,3*S*,5*S*) diastereomer has the following characteristics: ^{1}H NMR δ 0.65 (d, 3H, *J* = 6.4 Hz), 0.76 (d, 3H, *J* = 6.4 Hz),1.29−1.56 (m, 3H), 2.81 (m, 1H), 3.68 (m, 2H), 3.63 (S, 3H), 4.20 (m, 1H), 4.48 (d, 1H, *J* = 3.3 Hz), 4.53 (d, 1H, *J* = 3.3 Hz), 4.56 (dd, 1H, *J* = 4.8, 46.0 Hz), 7.26−7.55 (two set of m, 20H); ^{13}C NMR δ 20.0, 22.3, 24.7, 35.1, 44.0 (d, ^2J = 20.2 Hz), 50.7, 56.0, 69.8, 71.1, 72.2, 93.9 (d, ^1J = 188.9 Hz), 125.5, 126.5, 127.8, 136.7, 145.1, 171.4, 205.7 (d, ^2J = 28.8 Hz); FTIR (neat) 2957, 1735 (br), 704 cm^{-1}.

(2*S*,3*R*,5*S*)-Trityl-LeuΨ[COCFH]Ala-OMe, 11aa. General Procedure. The same procedure was used with **6aa** except that the base was changed to LDA and the enolate was generated at 0 °C. The ^{1}H NMR of the intermediate TMS-enol ether shows two pairs of doublets in the vinylic region and two methoxy singlets. The ratio is 2.0:1.0, and the signals of the minor isomer are identical to those of (*Z*)-TMS-enol ether **10aa**. The major isomer was assigned as (*E*)-TMS enol ether **14aa**. Fluorination of the mixture was carried out as described above: yield 60% of a colorless oil together with about 40% recovered starting material after flash chromatography (hexane/ethyl ether = 85:2.5); de 2.0:1.0 base on ^{1}H NMR of the crude product. The major diastereomer (2*S*,3*R*,5*S*) has the following characteristics: $[\alpha]^{25}_D$ +59.9 (*c* 0.546, $CHCl_3$); ^{1}H NMR δ 0.84 (d, 3H, *J* = 4.0 Hz), 0.90 (d, 3H, *J* = 4.5 Hz), 0.97 (d, 3H, *J* = 6.2 Hz), 1.52 (m, 2H), 1.78 (m, 1H), 2.53 (m, 1H), 2.93 (br, 1H), 3.65 (s, 3H), 3.87 (m, 1H), 4.61 (dd, 1H, *J* = 5.4, 45.0 Hz), 7.21−7.50 (two set of m, 15H); ^{13}C NMR δ 17.0, 27.6, 27.8, 29.1, 46.0 (d, ^2J = 20.2 Hz), 47.8, 56.4, 63.7, 75.7, 98.9 (d, ^1J = 186.7 Hz), 130.9, 132.4, 133.4, 150.7, 176.6, 202.8 (d, ^2J = 22.4 Hz); FTIR (neat) 2947, 1740, 1726, 709 cm^{-1}. Anal. Calcd for $C_{30}H_{34}O_3NF\cdot 0.5H_2O$: C, 71.69; H, 7.42; N, 2.79. Found: C, 71.67; H, 7.27; N, 2.66.

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