# Synthesis of a Peptidyl Difluoro Ketone Bearing the Aspartic Acid Side Chain: An Inhibitor of Interleukin-1β Converting Enzyme

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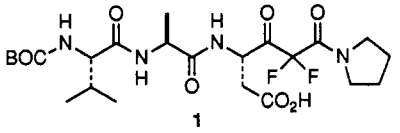
The synthesis of the peptidyl difluoro ketone **1**, an inhibitor of interleukin-1β converting enzyme (ICE), was accomplished by a route beginning with the reaction of $BrZnCF_2CO_2Et$ (**2**) with (2*S*)-1-(*tert*-butyldimethylsilyl)-4-oxo-2-azetidinecarboxaldehyde (**3**) to give a mixture of epimeric alcohols **4** and **5**. Conversion of alcohol **5** to **1** was carried out by a sequence including the novel coupling of β-lactam **17** and BOC-Ala-O(succinimide) to form lactone **18**. An early attempt to synthesize **1** utilized the β-lactam ketone **10** obtained in two steps from either **4** or **5**. This underwent addition of ethanol and stereoselective migration of the *tert*-butyldimethylsilyl group to afford the mixed silyl ethyl ketal **12**. Unfortunately, efforts to open the β-lactam ring of **12** and couple the intermediate β-amino ester **14** to BOC-Ala-O(succinimide) were complicated by an unexpected cyclization reaction. The difluoro ketone **1** was found to exist as a mixture of diastereomeric γ-hydroxy lactone tautomers in chloroform solution.

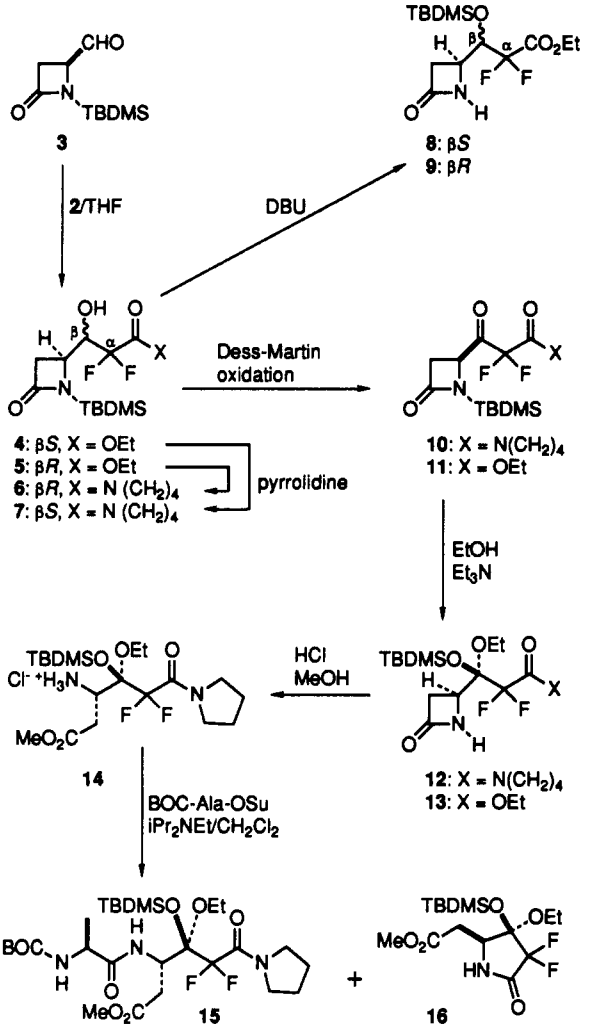
A promising approach to the discovery of new anti arthritic drugs is to inhibit the enzyme involved in maturation of the inflammatory cytokine interleukin-1β (IL-1β).[1] The enzyme, interleukin-1β converting enzyme (ICE), produces active, mature IL-1β by specific proteolytic cleavage between the aspartic acid(116) and alanine(117) residues of the IL-1β precursor protein.[2,3] This paper describes a route to the synthesis of peptidyl difluoroketones designed as inhibitors of ICE.[4] The approach is exemplified by the synthesis of **1**[5] which contains elements of the $P_3$ to $P_2'$ residues of the natural substrate including the aspartic acid side chain at $P_1$ essential for recognition by ICE.[2,6,7]



**1**

Peptidyl difluoro ketones designed as inhibitors of other enzymes (e.g., renin) typically contain nonfunctionalized side chains at $P_1$ and are invariably prepared by coupling of an α-amino aldehyde derivative with $BrZnCF_2CO_2Et$ (**2**).[8-10] Unfortunately, our attempts to couple the benzyl and *tert*-butyl esters of BOC-L-aspartic α-semialdehyde with **2** (generated by ultrasound in situ in the presence of

**Scheme I**




(1) For a recent review on IL-1 see: Dinarello, C. A. *Blood* **1991**, *77*, 1627.

(2) Thornberry, N. A.; Bull, H. G.; Calaycay, J. R.; Chapman, K. T.; Howard, A. D.; Kostura, M. J.; Miller, D. K.; Molineaux, S. M.; Weidner, J. R.; Aunins, J.; Elliston, K. O.; Ayala, J. M.; Casano, F. J.; Chin, J.; Ding, G. J.-F.; Egger, L. A.; Gaffney, E. P.; Limjuco, G.; Palyha, O. C.; Raju, S. M.; Rolando, A. M.; Salley, J. P.; Yamin, T.-T.; Lee, T. D.; Shively, J. E.; MacCross, M.; Mumford, R. A.; Schmidt, J. A.; Tocci, M. J. *Nature* **1992**, *356*, 768.

(3) Cerretti, D. P.; Kozlosky, C. J.; Mosley, B.; Nelson, N.; Van Ness, K.; Greenstreet, T. A.; March, C. J.; Kronheim, S. R.; Druck, T.; Cannizzaro, L. A.; Huebner, K.; Black, R. A. *Science* **1992**, *256*, 97.

(4) (a) ICE is classified as a cysteine protease (ref 2). For a recent review on inhibitors of cysteine proteases, see: Shaw, E. *Adv. Enzym.* **1990**, *63*, 271. (b) For a recent general review on protease inhibitors, see: Rich, D. H. In *Comprehensive Medicinal Chemistry*; Sammes, P. G., Ed.; Pergamon Press: London, 1990; Vol. 2, p 391.

(5) A related peptidic aldehyde is potent reversible inhibitor of ICE: Chapman, K. T. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 613 and ref 2. Our interest in preparing difluoro ketones as inhibitors of ICE was spurred by a desire to discover compounds other than aldehydes which would reversibly inactivate the enzyme.

(6) (a) Sleath, P. R.; Hendrickson, R. C.; Kronheim, S. R.; March, C. J.; Black, R. A. *J. Biol. Chem.* **1990**, *265*, 14526. (b) Howard, A. D.; Kostura, M. J.; Thornberry, N.; Ding, G. J. F.; Limjuco, G.; Weidner, J.; Salley, J. P.; Hogquist, K. A.; Chaplin, D. D.; Mumford, R. A.; Schmidt, J. A.; Tocci, M. J. *J. Immunol.* **1991**, *147*, 2964.

(7) For definitions of the notations $P_1$, $P_1'$, etc., see ref 4b.

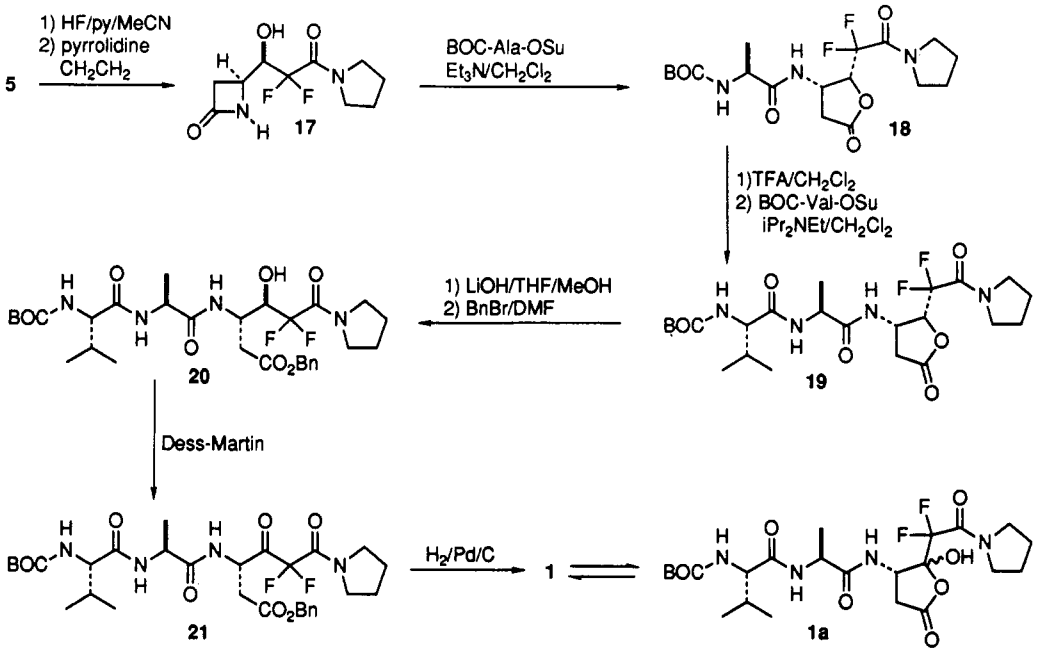
(8) Thaisrivongs, S.; Pals, D. T.; Kati, W. M.; Turner, S. R.; Thomasco, L. M.; Watt, W. *J. Med. Chem.* **1986**, *29*, 2080.

(9) Sham, H. L.; Rempel, C. A.; Stein, H.; Cohen, J. *J. Chem. Soc., Chem. Commun.* **1990**, 904.

(10) Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.* **1990**, *33*, 394.

0022-3263/92/1957-7309$03.00/0 

**Scheme II**




the aldehyde) were not successful.[11] An alternative approach was to examine L-aspartic $\alpha$-semialdehyde equivalents in the coupling; particularly attractive was the enantiomerically pure $\beta$-lactam aldehyde **3** (Scheme I).[12] This compound reacted smoothly with **2** to afford the crystalline epimeric alcohols **4** and **5** in a 1:2 ratio (70–80% yield) and in at least 94% enantiomeric purity.[13] After chromatographic separation of the products, the structure of **5** was established unambiguously by X-ray crystallographic analysis.[14] The relative stereochemistry of the major product (**5**) is the same as that for the reactions of **2** with acyclic $\alpha$-amino aldehyde derivatives (e.g., BOC-L-leucinal).[8]

To minimize separate advancement of intermediates **4** and **5**, a route to **1** involving early hydroxyl group oxidation was initially explored. In the first step, **4** and **5** were individually converted to the corresponding amides **7** and **6** by treatment with pyrrolidine in $CH_2Cl_2$.[15] Oxidation of either **6** or **7** with the Dess–Martin reagent[16] then provided the ketone **10** in high yield. Protection of the ketone carbonyl was achieved in a reaction suggested from attempts to derivatize either the alcohol or ester group of **5**. During these studies we noted a tendency for the TBDMS group to migrate onto the hydroxyl oxygen in the presence of base. Thus, in one experiment, exposure of **5** to DBU in toluene resulted in complete formation of the TBDMS ether **9** after 2.5 h at 23 °C.[17] We therefore reasoned that a hemiketal derived from **10** and an alcohol might similarly undergo TBDMS group migration to produce an intermediate in which the ketone carbonyl is protected as a mixed alkyl silyl ketal. Indeed, when dissolved in ethanol containing $Et_2N$ at 23 °C, **10** rapidly gave rise to the mixed ketal **12** as the only product (86%). The stereochemistry of **12** was inferred from the X-ray crystal structure of **13**,[14] the product obtained in 94% yield by similar treatment of the keto ester **11** with $Et_3N$/EtOH.[18] There being little reason to expect completely face-selective attack by EtOH on the ketone carbonyl in either **10** or **11**, the exclusive formation of **12** and **13** in these reactions appears to occur because only one of the two hemiketal diastereomers arising by initial reversible reaction with the alcohol undergoes silyl group transfer. Assuming the transfer occurs intramolecularly, the difference in reactivity between hemiketal diastereomers can be accounted for by an unfavorable steric interaction (apparent on inspection of models) between the $CF_2CO$ group and the cis hydrogen atom of the $\beta$-lactam methylene in the nonproductive isomer. In agreement with this argument, the alcohol **4** is relatively unreactive since formation of the TBDMS ether **8** occurs at a significant rate only at elevated temperature (DBU/benzene/80 °C).

(11) While starting aldehyde was consumed, no product arising from the desired coupling could be isolated. The use of preformed **2** (Altenburger, J. M.; Schirlin, D. *Tetrahedron Lett.* **1991**, *32*, 7255) in these reactions was not investigated.

(12) Labia, R.; Morin, C. *Chem. Lett.* **1984**, 1007.

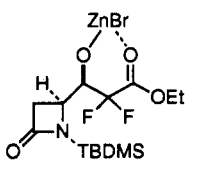
(13) Enantiomeric purity was assessed by $^1$H NMR in a concentrated benzene solution of (*S*)-(+)-2,2,2-(trifluoromethyl)-1-(9-anthryl)ethanol (Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263). The spectra (in particular the upfield singlets arising from the diastereotopic methyl groups on silicon) were compared to those of racemic samples of **4** and **5** in which well-resolved additional peaks were apparent.

(14) X-ray analyses of **5** and **13** were performed by Dr. J. Bordner, Central Research Division, Pfizer Inc, Eastern Point Rd., Groton, CT 06340. Atomic coordinates for these structures have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(15) As a result of competing base-catalyzed nitrogen to hydroxyl oxygen silyl group migration (vide infra), the yield of **6** (66%) was lower than that of **7** (94%).

(16) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.*, **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (c) Linderman, R. J.; Graves, D. M. *Tetrahedron Lett.* **1987**, *28*, 4259.

(17) Silyl group migration was also noted in the presence of pyrrolidine (ref 15). In contrast, the compounds expected from TBDMS group migration (i.e., **8** and **9**) were not detected in the reaction of the aldehyde **3** with **2**. This may be due to formation of a stable zinc chelate (i).




(i)

(18) Attempted reactions of **13** with pyrrolidine failed to give **12**. Using 2 equiv of pyrrolidine in methylene chloride no reaction occurred. Reaction took place at 50 °C in toluene using 20 equiv of the amine, but loss of the mixed ethyl silyl ketal group was apparent in the $^1$H NMR spectrum of the crude product mixture.

At this stage opening of the β-lactam ring was planned in order to incorporate the N-terminal amino acid residues. However, after exposure of **12** to HCl/MeOH[19] and coupling of the intermediate **14** with BOC-L-alanine *N*-hydroxysuccinimide ester, the yield of the desired product **15** was only 9%. The major product (61%) was the 2-pyrrolidinone derivative **16** resulting from intramolecular attack of the free amino group on the pyrrolidine amide.[20] This tendency of **14** to cyclize under conditions for amino acid coupling was unexpected based on literature accounts in which *N*-BOC-4-alkyl-4-amino-2,2-difluoro-3-hydroxybutyric acid derivatives (*N*-BOC-difluorostatines) are deprotected (TFA) and coupled with amino acid derivatives without incident.[8,10,21] Although the intermediacy of **14** could potentially be avoided by carrying out acylation of the β-lactam nitrogen of **12** prior to ring opening, an investigation of this possibility proved unsuccessful.[22]

In light of these results, we returned to intermediate **5** and pursued a route wherein hydroxyl group oxidation is carried out at a late stage. This approach, ultimately leading to **1**, is shown in Scheme II. The conversion of **5** to the amide **17** was most efficiently accomplished by deprotection ($HF/py/CH_3CN$) followed by reaction with pyrrolidine in $CH_2Cl_2$. The next step providing the lactone **18** directly from **17** achieved the goal of *direct coupling without prior β-lactam ring opening*. The reaction is presumed to occur via acylation on nitrogen, attack by *N*-hydroxysuccinimide on the β-lactam carbonyl, and lactonization of the resulting activated γ-hydroxy ester. After N-terminal extension of **18** to the peptidic lactone **19**, the lactone ring was cleaved with lithium hydroxide and the intermediate carboxylate salt was alkylated (benzyl bromide/DMF) to yield the γ-hydroxy ester **20**. Oxidation of the hydroxyl group was effected cleanly with the Dess–Martin reagent affording **21** which, fearing epimerization α to the ketone carbonyl under conditions for purification, was used directly in the final step (hydrogenolysis of the benzyl ester) yielding **1**.

In addition to the potential for the target compound (**1**) to exist as its hydrate, the reversible formation of the diastereomeric hydroxy-γ-lactone tautomers (**1a**) was considered a likely possibility[23,24] and was suspected upon examination of the $^1H$ NMR spectrum of the material in $CDCl_3$. The spectrum showed two species to predominate and resembled that of the intermediate lactone **19**. Most noteworthy was the appearance of the signals assigned to the protons of the lactone methylene group. In the spectrum of **19**, these protons give rise to two doublets of doublets at 2.64 ($J$ = 8.3, 18.1 Hz) and 2.87 ppm ($J$ = 9.8, 18.1 Hz), characteristic for protons in an AMX system. In the spectrum of **1**, two overlapping sets of AMX doublets of doublets were observed having chemical shifts and coupling constants in close agreement to those for **19**. In contrast, compounds **20** and **21** gave rise to second-order (ABX) patterns for the corresponding methylene protons, a result of the higher degree of conformational freedom allowed for the nonlactonized side chain.

That the ketone form (**1**) is not a major species in chloroform was also suggested by $^{13}C$ NMR spectroscopy. As with $^1H$ NMR, the $^{13}C$ NMR spectrum of the material in $CDCl_3$ exhibited a set of signals correlating well with those for the precursor lactone **19**; the doubling of several signals again suggested diastereomers to be present.[25] Unfortunately, while no low-field resonance characteristic of ketone functionality was observed, the expected signal for a ketal quaternary carbon atom could not be unambiguously assigned.[26]

Finally, the IR spectrum of **1** in chloroform showed a strong band at 1812 $cm^{-1}$ characteristic of a γ-lactone (e.g., **19**). This result, along with the NMR data, convincingly argues in favor of the diastereomeric hydroxy-γ-lactone tautomers (**1a**) predominating in chloroform solution.[27]

While **1** exists as **1a** in chloroform, we had no information on its behavior in water.[28] Nonetheless, since an equilibrium between **1** and the other species was considered likely in an aqueous medium, we anticipated that ICE inhibition would occur regardless of which form predominates under the assay conditions. Indeed, the compound was significantly active in a system developed to test inhibitor activity against ICE.[29] Details of the activity of **1** and its analogues will be published elsewhere. In addition to being useful for the preparation of peptidyl difluoro ketones in the series exemplified by **1**, the chemistry presented here should be applicable to the synthesis of potential protease inhibitors of other structural classes bearing an aspartic acid side chain at $P_1$.

## Experimental Section

Anhydrous THF, DMF, and $CH_2Cl_2$ were obtained from Aldrich Chemical Co., Inc., in Sure/Seal bottles opened immediately prior to use. Other solvents and reagents were of reagent grade and were used as supplied by the manufacturer. Organic extracts were routinely dried over anhydrous $MgSO_4$. Chromatography refers

(19) Hauser, F. M.; Ellenberger, S. R.; Rhee, R. P. *J. Org. Chem.* **1987**, *52*, 5041.

(20) Products arising from exchange of ethoxy for methoxy were not detected, nor were products resulting from epimerization at the ketal center.

(21) Fearon, K.; Spaltenstein, A.; Hopkins, P. B.; Gelb, M. H. *J. Med. Chem.* **1987**, *30*, 1617.

(22) No reaction occurred on attempted acylation of **12** with BOC-L-alanine *N*-hydroxysuccinimide ester or the mixed anhydride derived from BOC-L-alanine and isobutylchloroformate (Campbell, M. M.; Carruthers, N. I.; Mickel, S. J. *Tetrahedron*, **1982**, *38*, 2513). In view of the successful acylation of **17** (vide infra), the failure of **12** to react under these conditions could be a consequence of steric hindrance by the adjacent ketal center.

(23) Carling, R. W.; Clark, J. S.; Holmes, A. B.; Sartor, D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 95.

(24) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813.

(25) Although other explanations for the doubling of peaks in the NMR spectra were considered (e.g., that **1** rapidly epimerizes α to the ketone carbonyl, but remains in the open form), the only one fully consistent with all the data is that **1** exists as a mixture of diastereomeric hydroxy-γ-lactone tautomers (**1a**) in chloroform solution and that epimerization, if it occurs at all, is very slow in this solvent. No changes in the NMR spectra were evident after **1** was allowed to stand in $CDCl_3$ for a few days or even following chromatography on silica gel using 1:5:94 $AcOH/MeOH/CHCl_3$ as eluant. However, after chromatography using 5:95 $MeOH/CHCl_3$ as eluant, further multiplication of signals in the NMR spectra was noted. In particular, the signals in the $^1H$ NMR spectrum assigned to the lactone methylene protons became significantly more complex and, in the $^{13}C$ NMR spectrum, the signal centered at 34 ppm assigned to the corresponding lactone carbon atom was no longer doubled but was *quadrupled*. These observations strongly suggest that epimerization at the position α to the ketone carbonyl took place and lend additional support for the stereochemical integrity of the material prior to the $MeOH/CHCl_3$ chromatography.

(26) A broad peak centered at 104 ppm, in the range expected for the ketal carbon atom, was observed but diagnostic carbon–fluorine coupling was not resolved. The spectrum of **1** in $CD_3OD$ displayed a weak triplet at 98.7 ppm ($J$ = 24 Hz, C–F coupling) which was supportive of either the hydroxy-γ-lactone, hydrate, or methyl hemiketal forms. As in the spectrum in $CDCl_3$, no resonance above 180 ppm was apparent.

(27) This result contrasts the recent finding that 4,5-dioxohexanoic acid exists mainly as the open keto acid tautotomer in chloroform (ref 23) but is in agreement with the behavior of 2-benzyl-4-oxo-5,5,5-trifluoropentanoic acid in this solvent (ref 24).

(28) Considering that 2-benzyl-4-oxo-5,5,5-trifluoropentanoic acid exists in aqueous solution near neutrality as the open, monoanionic hydrate (ref 24), similar behavior of **1** in water was expected.

(29) Arriola, M. W.; Carty, T. J.; Danley, D. E.; Daumy, G. O.; Downs, J. T.; LaLiberte, R. E.; McColl, A. S.; Otterness, I. G.; Wilder, C. Unpublished work from Pfizer Inc. The assay uses partially purified human ICE from THP-1 cells. The substrate is a component of diluted human peripheral blood monocyte lysates containing standard enzyme inhibitors.

to "flash chromatography" on Baker silica gel 40-μm flash chromatography packing. IR spectra ($\nu_{max}$) were recorded in $CHCl_3$ solutions. NMR spectra were recorded in $CDCl_3$ at 250 MHz ($^1H$).

**Ethyl [*S*-(*R**,*R**)]-1-[(1,1-Dimethylethyl)dimethylsilyl]-α,α-difluoro-β-hydroxy-4-oxo-2-azetidinepropanoate (4) and Ethyl [*R*-(*R**,*S**)]-1-[(1,1-Dimethylethyl)dimethylsilyl]-α,α-difluoro-β-hydroxy-4-oxo-2-azetidinepropanoate (5).** To a solution of freshly prepared crude (2*S*)-1-[(1,1-dimethylethyl)dimethylsilyl]-4-oxo-2-azetidinecarboxaldehyde (3)[12] (10.3 g, 48.3 mmol) and ethyl bromodifluoroacetate (25.0 g, 123 mmol) in anhydrous THF (100 mL) was added Zn powder (10.5 g, 161 mmol). The reaction flask was placed in a sonicating bath at 35 °C for 40 min with occasional manual agitation. The mixture was then poured into ice/$H_2O$, and the resulting slurry was filtered through Celite, washing well with $Et_2O$. The aqueous layer was separated and extracted with $Et_2O$. The crude product mixture, obtained from the combined organic layers, was determined to contain the epimeric products 4 and 5 in a ratio of approximately 1:2 by $^1H$ NMR. The mixture was chromatographed on silica gel using 3:7 EtOAc/hexane as eluant. Complete separation of the epimeric products 4 and 5 was not achieved. Fractions containing only the less polar product provided a solid which was triturated with hexane leaving pure 5 as white crystals (5.17 g, 31.5%): mp 91–93 °C; $[\alpha]^{20}_D$ −10.6° (*c* 1.13, $CHCl_3$); $\nu_{max}$ 3578, 1747 $cm^{-1}$; $^1H$ NMR δ 0.24, 0.26 (2 × s, 2 × 3 H, $Me_2Si$), 0.96 (s, 9 H, *t*-Bu), 1.37 (t, 3 H, *J* = 7.2 Hz, $CH_2Me$), 2.88 (br d, 1 H, *J* = 15.9 Hz, CHCON), 3.00 (br s, 1 H, OH), 3.21 (dd, 1 H, *J* = 5.6, 15.9 Hz, CHCON), 3.78 (m, 1 H, $CHCH_2CO$), 4.37 (m, 1 H, $CHCF_2$), 4.37 (q, 2 H, *J* = 7.2 Hz, $CH_2Me$); $^{13}C$ NMR δ −5.1, −5.0, 13.8, 18.5, 26.3, 40.9, 48.8 (t, *J* = 3 Hz), 63.3, 75.2 (t, *J* = 25 Hz), 114.3 (t, *J* = 258 Hz), 163.0 (t, *J* = 32 Hz), 172.9; MS (FAB) *m/z* 338 ($MH^+$, 100). Anal. Calcd for $C_{14}H_{25}F_2NO_4Si$: C, 49.83; H, 7.47; N, 4.12. Found: C, 49.90; H, 7.28; N, 4.15.

Fractions containing only the more polar product provided a solid which was triturated with hexane leaving pure 4 as white crystals (1.26 g, 7.7%): mp 101–103 °C; $[\alpha]^{20}_D$ −54.8° (*c* 1.70, $CHCl_3$); $\nu_{max}$ 3669, 1738 $cm^{-1}$; $^1H$ NMR δ 0.25, 0.29 (2 × s, 2 × 3 H, $Me_2Si$), 0.97 (s, 9 H, *t*-Bu), 1.38 (t, 3 H, *J* = 7.2 Hz, $CH_2Me$), 2.8 (br s, 1 H, OH), 3.01 (dd, 1 H, *J* = 5.5, 15.6 Hz, CHCON), 3.23 (br d, 1 H, *J* = 15.6 Hz, CHCON), 3.92 (m, 1 H, $CHCH_2CO$), 4.40 (m, 1 H, overlapped, $CHCF_2$), 4.40 (q, 2 H, *J* = 7.2 Hz, $CH_2Me$); $^{13}C$ NMR δ −5.8, −5.6, 13.9, 18.5, 26.1, 38.3, 47.9, 63.4, 70.0 (t, *J* = 26 Hz), 114.1 (t, *J* = 256 Hz), 163.1 (t, *J* = 33 Hz), 173.4; MS (FAB) *m/z* 338 ($MH^+$, 100). Anal. Calcd for $C_{14}H_{25}F_2NO_4Si$: C, 49.83; H, 7.47; N, 4.12. Found: C, 49.93; H, 7.39; N, 4.15.

Mixed fractions containing 4 and 5 were combined with the liquors from trituration to yield a pale yellow oil (5.15 g, 31.5%) from which additional amounts of pure 4 and 5 were obtained by repetition of the above separation procedure.

**[*R*-(*R**,*S**)]-1-[3-[1-[(1,1-Dimethylethyl)dimethylsilyl]-4-oxo-2-azetidinyl]-2,2-difluoro-3-hydroxy-1-oxopropyl]-pyrrolidine (6).** Pyrrolidine (1.6 mL, 19.2 mmol) was added to a solution of the β-lactam alcohol 5 (3.01 g 8.92 mmol) in anhydrous $CH_2Cl_2$ (22 mL) at 0 °C. After the solution was stirred for 0.25 h at 0 °C, the cooling bath was removed and stirring was continued at 23 °C for 4 h. The reaction mixture was passed through a pad of silica gel, washing with EtOAc, the solvent was evaporated, and the residue was chromatographed on silica gel using 3:7 EtOAc/hexane and then 1:1 EtOAc/hexane as eluant. Fractions containing only 6 gave a white crystalline solid, 2.13 g (66%): mp 135–138 °C, $[\alpha]^{20}_D$ −56.4° (*c* 2.73, $CH_2Cl_2$); $\nu_{max}$ 3476, 1731, 1643 $cm^{-1}$; $^1H$ NMR δ 0.27, 0.28 (2 × s, 2 × 3 H, $Me_2Si$), 0.98 (s, 9 H, *t*-Bu), 1.85–2.04 (m, 4 H, 2 × $CH_2CH_2N$), 2.89 (dt, 1 H, *J* = 2.7, 15.7 Hz, CHCON), 3.19 (dd, 1 H, *J* = 5.7, 15.7 Hz, CHCON), 3.53 (m, 2 H, 2 × $CH_2CHN$), 3.71 (m, 2 H, 2 × $CH_2CHN$), 3.84 (m, 1 H, $CHCH_2CO$), 3.96 (m, 1 H, OH), 4.10 (m, 1 H, $CHCF_2$); $^{13}C$ NMR δ −5.0, −4.8, 18.5, 23.2, 26.3, 26.5, 41.2 (d, *J* = 4 Hz), 46.5 (t, *J* = 6 Hz), 47.3, 48.5 (d, *J* = 5 Hz), 75.3 (dd, *J* = 23, 26 Hz), 115.6 (dd, *J* = 259, 266 Hz), 161.9 (t, *J* = 29 Hz), 172.5; MS (FAB) *m/z* 363 ($MH^+$, 100). Anal. Calcd for $C_{16}H_{28}F_2N_2O_3Si$: C, 53.02; H, 7.79; N, 7.73. Found: C, 52.79; H, 7.59; N, 7.62.

**[*S*-(*R**,*R**)]-1-[3-[1-[(1,1-Dimethylethyl)dimethylsilyl]-4-oxo-2-azetidinyl]-2,2-difluoro-3-hydroxy-1-oxopropyl]-pyrrolidine (7).** Pyrrolidine (0.6 mL, 7.2 mmol) was added to a solution of the β-lactam alcohol 4 (508 mg, 1.51 mmol) in toluene (5 mL) at 23 °C. After the solution was stirred at 25 °C for 0.75 h, the solvent was evaporated and the residue was chromatographed on silica gel using 4:6 EtOAc/hexane as eluant. Fractions containing only 7 gave a white crystalline solid, 514 mg (94%): mp 119–121 °C; $[\alpha]^{20}_D$ −46.0° (*c* 1.74, $CH_2Cl_2$); $\nu_{max}$ 3484, 1731, 1645 $cm^{-1}$; $^1H$ NMR δ 0.25, 0.26 (2 × s, 2 × 3 H, $Me_2Si$), 0.97 (s, 9 H, *t*-Bu), 1.86–2.01 (m, 4 H, 2 × $CH_2CH_2N$), 2.97 (dd, 1 H, *J* = 5.5, 15.4 Hz, CHCON), 3.32 (dt, 1 H, *J* = 2.2, 15.4 Hz, CHCON), 3.53 (m, 2 H, 2 × $CH_2CHN$), 3.71 (m, 3 H, 2 × $CH_2CHN$, OH), 3.95 (m, 1 H, $CHCH_2CO$), 4.45 (dt, 1 H, *J* = 4.5, 22 Hz, $CHCF_2$); $^{13}C$ NMR δ −6.0, −5.6, 18.4, 23.2, 26.1, 26.3, 38.4, 46.5 (dd, *J* = 5, 7 Hz), 47.4, 69.4 (dd, *J* = 23, 27 Hz), 115.9 (dd, *J* = 258, 265 Hz), 161.7 (t, *J* = 28 Hz), 173.4; MS (FAB) *m/z* 363 ($MH^+$, 100). Anal. Calcd for $C_{16}H_{28}F_2N_2O_3Si$: C, 53.02; H, 7.79; N, 7.73. Found: C, 52.94; H, 7.79; N, 7.78.

**Ethyl [*S*-(*R**,*R**)]-β-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-α,α-difluoro-4-oxo-2-azetidinepropanoate (8).** A solution of the β-lactam alcohol 4 (250 mg, 0.74 mmol) and DBU (136 mg, 0.89 mmol) in benzene (30 mL) was heated at reflux for 1.5 h. After cooling, the mixture was passed through a pad of silica gel, washing with EtOAc. The solvents were evaporated to leave a residue which was chromatographed on silica gel eluting with 4:6 EtOAc/hexane. Fractions containing 8 were combined and concentrated to give an oil, 104 mg (42%): $[\alpha]^{20}_D$ −40.7° (*c* 1.70, $CH_2Cl_2$); $\nu_{max}$ 3411, 1766 $cm^{-1}$; $^1H$ NMR δ 0.07 (s, 6 H, $Me_2Si$), 0.83 (s, 9 H, *t*-Bu), 1.31 (t, 3 H, *J* = 7.2 Hz, $CH_2Me$), 2.92 (m, 2 H, CHCON), 3.90 (m, 1 H, $CHCH_2CO$), 4.12 (m, 1 H, $CHCF_2$), 4.28 (q, 2 H, *J* = 7.2 Hz, $CH_2Me$), 6.33 (br s, 1 H, NH); $^{13}C$ NMR δ −5.1, −4.8, 13.8, 18.0, 25.5, 40.0, 47.0 (d, *J* = 3 Hz), 63.2, 73.1 (t, *J* = 26 Hz), 114.2 (t, *J* = 256 Hz), 162.8 (t, *J* = 31 Hz), 167.9; MS (FAB) *m/z* 338 ($MH^+$, 100), 296 (23), 280 (19), 238 (31); HRMS (FAB) calcd for $C_{14}H_{26}F_2NO_4Si$ ($MH^+$) 338.1600, found 338.1623.

**Ethyl [*R*-(*R**,*S**)]-β-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-α,α-difluoro-4-oxo-2-azetidinepropanoate (9).** A solution of the β-lactam alcohol 5 (150 mg, 0.44 mmol) and DBU (68 mg, 0.44 mmol) in anhydrous $CH_2Cl_2$ (15 mL) was stirred at 23 °C for 2 h. After the mixture was passed through a pad of silica gel (washing with EtOAc), the solvents were evaporated. The residue was chromatographed on silica gel eluting with 4:6 EtOAc/hexane to yield 9 as an oil, 126 mg (84%): $[\alpha]^{20}_D$ +11.3° (*c* 1.54, $CH_2Cl_2$); $\nu_{max}$ 3423, 1768 $cm^{-1}$; $^1H$ NMR δ 0.10 (s, 6 H, $Me_2Si$), 0.85 (s, 9 H, *t*-Bu), 1.33 (t, 3 H, *J* = 7.2 Hz, $CH_2Me$), 2.76 (br d, 1 H, *J* = 15.2 Hz, CHCON), 3.07 (ddd, 1 H, *J* = 2.3, 4.9, 15.2 Hz, CHCON), 3.95–4.06 (m, 2 H, $CHCF_2$, $CHCH_2CO$), 4.30 (m, 2 H, $CH_2Me$), 6.16 (br s, 1 H, NH); $^{13}C$ NMR δ −4.8, 13.8, 18.0, 25.5, 40.7, 47.1 (dd, *J* = 2.9, 5.8 Hz), 63.2, 74.6 (t, *J* = 26 Hz), 114.2 (dd, *J* = 256, 259 Hz), 163.0 (t, *J* = 31 Hz), 166.9; MS (EI) 337 ($M^+$, 23), 238 (100), 210 (50); HRMS calcd for $C_{14}H_{25}F_2NO_4Si$ 337.1521, found 337.1488.

**(*S*)-1-[3-[1-[(1,1-Dimethylethyl)dimethylsilyl]-4-oxo-2-azetidinyl]-2,2-difluoro-1,3-dioxopropyl]pyrrolidine (10).** To a solution of the β-lactam alcohol 7 (2.08 g, 5.74 mmol) in anhydrous $CH_2Cl_2$ (130 mL) at 23 °C was added the Dess–Martin reagent (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one) (9.0 g, 21.2 mmol). The resulting heterogeneous mixture was stirred at 23 °C for 16 h and then quenched by addition of EtOAc and a solution of sodium thiosulfate (33 g) in saturated $NaHCO_3$ solution (300 mL). After the mixture was stirred for about 15 min when all solids had dissolved, the aqueous layer was separated and extracted with EtOAc. The combined EtOAc fractions were dried and concentrated to afford 10 as a clear oil (2.07 g, 100%): $^1H$ NMR δ 0.07, 0.29 (2 × s, 2 × 3 H, $Me_2Si$), 0.94 (s, 9 H, *t*-Bu), 1.91–2.02 (m, 4 H, 2 × $CH_2CH_2N$), 3.02 (dd, 1 H, *J* = 3.2, 15.4 Hz, CHCON), 3.43 (dd, 1 H, overlapped, *J* = 6.5, 15.4 Hz, CHCON), 3.49 (m, 2 H, 2 × $CH_2CHN$), 3.68 (m, 2 H, 2 × $CH_2CHN$), 4.64 (dd, 1 H, *J* = 3.2, 6.5 Hz, $CHCH_2CO$); $^{13}C$ NMR −6.3, −5.9, 14.2, 18.6, 23.2, 26.1, 44.5, 46.2 (t, *J* = 5 Hz), 47.3, 51.5, 110.7 (t, *J* = 269 Hz), 159.6 (t, *J* = 27 Hz), 170.1, 196.6 (t, *J* = 27 Hz); MS (FAB) *m/z* 379 ($M + H_3O^+$, 47), 361 ($MH^+$, 42), 319 (100).

Having a high degree of purity by $^1H$ NMR, the material was used immediately in the next step.

**Ethyl (*S*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-α,α-difluoro-β,4-dioxo-2-azetidinepropanoate (11).** To a solution

of the β-lactam alcohol **5** (1.00 g, 2.96 mmol) in anhydrous $CH_2Cl_2$ (50 mL) at 23 °C was added the Dess–Martin reagent (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one) (3.77 g, 8.9 mmol). The resulting heterogeneous mixture was stirred at 23 °C for 4 h and was then quenched by addition of $Et_2O$ and a solution thiosulfate (13.3 g) in saturated $NaHCO_3$ solution (110 mL). After the mixture was stirred for about 15 min when all solids had dissolved, the organic layer was separated, washed with additional saturated $NaHCO_3$ solution, dried, and evaporated to leave **11** as a clear oil (0.99 g, 100%): $\nu_{max}$ 1755 $cm^{-1}$; $^1H$ NMR δ 0.07, 0.31 (2 × s, 2 × 3 H, $Me_2Si$), 0.99 (s, 9 H, *t*-Bu), 1.38 (t, 3 H, *J* = 7.2 Hz, $CH_2$*Me*), 3.05 (dd, 1 H, *J* = 3.2, 15.2 Hz, CHCON), 3.52 (dd, 1 H, *J* = 6.6, 15.2 Hz, CHCON), 4.40 (q, 2 H, *J* = 7.2 Hz, C*H*$_2$Me), 4.69 (dd, 1 H, *J* = 3.2, 6.6 Hz, C*H*CH$_2$CO); $^{13}C$ NMR δ −6.5, −6.2, 13.5, 18.3, 26.0, 43.9, 50.8, 64.0, 108.1 (t, *J* = 264 Hz), 160.3 (t, *J* = 28 Hz), 169.0, 195.8 (t, *J* = 28 Hz); MS (FAB) *m/z* 354 (M + $H_3O^+$, 46), 336 ($MH^+$, 25), 281 (34), 221 (51), 207 (42), 147 (100).

Having a high degree of purity by $^1H$ NMR, the material was used immediately in the next step.

**[*R*-(*R**,*S**)]-1-[3-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-3-(4-oxo-2-azetidinyl)-2,2-difluoro-3-ethoxy-1-oxo-propyl]pyrrolidine (12).** Triethylamine (0.5 mL, 3.6 mmol) was added to a solution of the ketone **10** (523 mg, 1.45 mmol) in EtOH (25 mL) at 23 °C. The solution was stirred at 23 °C for 20 min and then concentrated to leave an oil. This was chromatographed on silica gel eluting with 8:2 EtOAc/hexane. Fractions containing **12** yielded a white crystalline solid, 509 mg (86%): mp 124–127 °C; $[\alpha]^{20}_D$ −58.2° (*c* 2.45, $CHCl_3$); $\nu_{max}$ 3424, 1764, 1644 $cm^{-1}$; $^1H$ NMR δ 0.20 (d, 3 H, *J* = 1.0 Hz, MeSi), 0.22 (d, 3 H, *J* = 1.7 Hz, MeSi), 0.93 (s, 9 H, *t*-Bu), 1.16 (t, 3 H, *J* = 7.0 Hz, $CH_2$*Me*), 1.77–2.02 (m, 4 H, 2 × C*H*$_2$CH$_2$N), 2.89 (ddd, 1 H, *J* = 1.7, 4.9, 14.2 Hz, CHCON), 3.14 (dd, 1 H, *J* = 1.1, 14.2 Hz, CHCON), 3.43–3.69 (m, 5 H, C*H*$_2$Me, 3 × CH$_2$C*H*N), 3.92 (dd, 1 H, *J* = 2.4, 4.8 Hz, C*H*CH$_2$CO), 3.98–4.02 (m, 1 H, overlapped, CH$_2$C*H*N), 6.08 (br s, 1 H, NH); $^{13}C$ NMR δ −3.6, 15.2, 18.9, 23.2, 26.4, 26.5 (d, *J* = 3 Hz), 39.9, 47.3 (d, *J* = 12 Hz), 48.0, 50.3, 58.5, 97.3 (dd, *J* = 21, 27 Hz), 115.1 (dd, *J* = 255, 271 Hz), 161.4 (t, *J* = 28 Hz), 166.6; MS (FAB) *m/z* 407 ($MH^+$, 100), 361 (41). Anal. Calcd for $C_{18}H_{32}F_2N_2O_4Si$: C, 53.18; H, 7.93; N, 6.89. Found: C, 53.09; H, 7.52; N, 6.76.

**Ethyl [*R*-(*R**,*S**)]-β-[[(1,1-Dimethylethyl)silyl]oxy]-β-ethoxy-α,α-difluoro-4-oxo-2-azetidinepropanoate (13).** Triethylamine (1.0 mL, 7.2 mmol) was added to a solution of the ketone **11** (0.99 g, 2.96 mmol) in EtOH (50 mL) at 23 °C. The solution was stirred at 23 °C for 20 min and then concentrated to leave an oil. This was chromatographed on silica gel eluting with 4:6 EtOAc/hexane. Fractions containing **13** yielded an oil which crystallized on standing, 1.06 g (94%): mp 54–56 °C; $[\alpha]^{20}_D$ −22.9° (*c* 2.28, $CH_2Cl_2$): $\nu_{max}$ 3425, 1767 $cm^{-1}$; $^1H$ NMR δ 0.15, 0.17 (2 × s, 2 × 3 H, $Me_2Si$), 0.86 (s, 9 H, *t*-Bu), 1.12 (t, 3 H, *J* = 6.8 Hz, OCH$_2$*Me*), 1.32 (t, 3 H, *J* = 6.9 Hz, CO$_2$CH$_2$*Me*), 2.96 (ddd, 1 H, *J* = 1.8, 5.0, 14.6 Hz, CHCON), 3.05 (ddd, 1 H, *J* = 1.6, 2.5, 14.6 Hz), 3.61 (m, 2 H, OC*H*$_2$Me), 4.05 (dd, 1 H, *J* = 2.5, 5.0 Hz, C*H*CH$_2$CO), 4.28 (m, 2 H, CO$_2$C*H*$_2$Me), 5.98 (br s, 1 H, NH); $^{13}C$ NMR δ −3.5, −3.2, 13.7, 15.2, 18.5, 25.6, 39.6, 49.4, 59.4, 63.2, 96.9 (t, *J* = 25 Hz), 114.1 (t, *J* = 265 Hz), 163.0 (t, *J* = 31 Hz), 167.3; MS (FAB) *m/z* 382 ($MH^+$, 100), 336 (24), 324 (17). Anal. Calcd for $C_{16}H_{29}F_2NO_5Si$: C, 50.38; H, 7.66; N, 3.67. Found: C, 50.56; H, 7.66; N, 3.76.

**Methanolysis of 12 and Coupling of 14 with BOC-L-Ala-OSu.** A solution of the β-lactam **12** (200 mg, 0.492 mmol) in MeOH was cooled in an ice bath. To this was added a chilled saturated solution of HCl in MeOH (20 mL). The reaction was stirred at 0 °C for 2 h at which point TLC (silica gel, EtOAc as eluant) showed some starting material remaining. Additional cold HCl/MeOH (20 mL) was added, and the ice bath was removed. After the solution was stirred at 23 °C for 40 min, volatiles were evaporated to leave **14** as an oil. This was dissolved in anhydrous $CH_2Cl_2$ (6 mL), and *N*-(*tert*-butoxycarbonyl)-L-alanine *N*-hydroxysuccinimide ester (170 mg, 0.593 mmol) and diisopropylethylamine (0.17 mL, 0.98 mmol) were sequentially added. The mixture was stirred at 23 °C for 3 h at which point TLC (1:1 EtOAc/hexane as eluant) showed no further change. The mixture was diluted with EtOAc, washed sequentially with 1 N HCl and saturated $NaHCO_3$ solutions, dried, and concentrated to afford a clear oil. This was chromatographed on silica gel eluting with 3:7 EtOAc/hexane. The major product **16** eluted first and afforded white crystals, 111 mg (61%). An analytical sample was prepared by trituration with hexane: mp 104–106 °C; $[\alpha]^{20}_D$ −43.7° (*c* 1.63, $CHCl_3$); $\nu_{max}$ 3417, 3326, 1756, 1732 $cm^{-1}$; $^1H$ NMR δ 0.21 (s, 6 H, $Me_2Si$), 0.91 (s, 9 H, *t*-Bu), 1.23 (t, 3 H, *J* = 7.1 Hz, $CH_2$*Me*), 2.53 (ddd, 1 H, *J* = 0.8, 10.2, 17.7 Hz, CHCO$_2$), 2.78 (dd, 1 H, *J* = 4.0, 17.7 Hz, CHCO$_2$), 3.68 (m, 2 H, C*H*$_2$Me), 3.72 (s, 3 H, overlapped, CO$_2$Me), 4.17–4.21 (m, 1 H, C*H*CH$_2$), 6.89 (br s, 1 H, NH); $^{13}C$ NMR δ −3.7 (d, *J* = 4 Hz), −3.6 (d, *J* = 4 Hz), 15.0, 18.4, 25.6, 36.3, 52.1, 52.9 (d, *J* = 2 Hz), 59.0, 98.1 (dd, *J* = 18, 23 Hz), 111.4 (dd, *J* = 253, 271 Hz), 164.3 (dd, *J* = 28, 31 Hz), 171.5; MS (FAB) *m/z* 368 ($MH^+$, 76), 322 (100), 310 (60), 236 (42). Anal. Calcd for $C_{15}H_{27}F_2NO_5Si$: C, 49.03; H, 7.41; N, 3.81. Found: C, 49.20; H, 7.49; N, 3.90.

The minor product **15**, eluted next, afforded a clear oil, 26 mg (9%): $^1H$ NMR δ 0.16 (d, 3 H, *J* = 2.6 Hz, MeSi), 0.21 (d, 3 H, *J* = 2.6 Hz, MeSi), 0.92 (s, 9 H, *t*-BuSi), 1.04 (t, 3 H, *J* = 7.0 Hz, OCH$_2$*Me*), 1.23 (d, 3 H, *J* = 6.9 Hz, NCH*Me*), 1.42 (s, 9 H, *t*-BuO), 1.70–2.00 (envelope, 4 H, 2 × C*H*$_2$CH$_2$N), 2.68–2.92 (m, 2 H, CH$_2$CO$_2$), 3.40–3.70 (envelope, 5 H, OC*H*$_2$Me, 3 × CH$_2$C*H*N), 3.63 (s, 3 H, overlapped, MeO), 4.00–4.20 (envelope, 2 H, NC*H*Me, CH$_2$C*H*N), 4.82 (m, 1 H, C*H*CH$_2$CO), 5.26 (br d, 1 H, *J* = 7.8 Hz, BOCNH), 7.15 (br d, 1 H, *J* = 8.8 Hz, NH); MS (FAB) *m/z* 610 (31, $MH^+$), 564 (100), 508 (41); HRMS (FAB) calcd for $C_{27}H_{50}F_2O_8Si$ 610.3337, found 610.3350.

**[*R*-(*R**,*S**)]-1-[3-(4-Oxo-2-azetidinyl)-2,2-difluoro-3-hydroxy-1-oxopropyl]pyrrolidine (17).** To a solution of the β-lactam alcohol **5** (1.0 g, 2.96 mmol) in $CH_3CN$ (20 mL) at 0 °C was added HF/pyridine (1.5 mL). The cooling bath was removed, and the mixture was stirred at 23 °C for 1.5 h. The mixture was diluted with $H_2O$ and then extracted with EtOAc (3×). The combined EtOAc extracts were dried and concentrated to afford ethyl [*R*-(*R**,*S**)]-α,α-difluoro-β-hydroxy-4-oxo-2-azetidinepropanoate as a pale orange oil, 636 mg (96%): $^1H$ NMR δ 1.32 (t, 3 H, *J* = 7.1 Hz, $CH_2$*Me*), 2.90 (br d, 1 H, *J* = 15.0 Hz, CHCON), 3.07 (ddd, *J* = 1.5, 4.9, 15.0 Hz, CHCON), 3.98 (envelope, 1 H, C*H*CH$_2$), 4.09 (dt, 1 H, *J* = 5.0, 18 Hz, CHCF$_2$), 4.33 (q, 2 H, J = 7.1 Hz, C*H*$_2$Me), 4.70 (br s, 1 H, OH), 6.99 (br s, 1 H, NH). This was dissolved in anhydrous $CH_2Cl_2$ (5 mL). The solution was cooled to 0 °C, pyrrolidine (0.27 mL, 3.2 mmol) was added, and the mixture was stirred at 23 °C for 2 h. After evaporation of the solvent, the residue was chromatographed on silica gel using 6:94 MeOH/$CHCl_3$ as eluant. Fractions containing only **17** yielded an oil which crystallized on standing, 535 mg (73% overall from **5**). An analytical sample was prepared by recrystallization from toluene: mp 104–106 °C; $[\alpha]^{20}_D$ +10.0° (*c* 2.08, $CH_2Cl_2$); $\nu_{max}$ 3416, 1766, 1646 $cm^{-1}$; $^1H$ NMR δ 1.79–2.00 (m, 4 H, 2 × C*H*$_2$CH$_2$N), 2.91 (br d, 1 H, *J* = 14.9 Hz, CHCON), 3.06 (ddd, 1 H, *J* = 0.8, 3.8, 14.9 Hz, CHCON), 3.50 (m, 2 H, 2 × CH$_2$C*H*N), 3.70 (m, 2 H, 2 × CH$_2$C*H*N), 3.98 (m, 1 H, C*H*CH$_2$CO), 4.14 (m, 1 H, CHCF$_2$), 4.61 (br s, 1 H, OH), 6.59 (br s, 1 H, NH); $^{13}C$ NMR δ 23.2, 26.3, 40.5, 46.1, 46.7 (t, *J* = 6 Hz), 47.6, 71.8 (dd, *J* = 25, 27 Hz), 116.1 (dd, *J* = 257, 262 Hz), 161.6 (t, *J* = 29 Hz), 168.3; MS (EI) *m/z* 249 ($MH^+$), 230 (21), 178 (59), 167 (31), 142 (50), 113 (25), 98 (100), 70 (88), 55 (51). Anal. Calcd for $C_{10}H_{14}F_2N_2O_3$: C, 48.39; H, 5.68; N, 11.29. Found: C, 48.51; H, 5.68; N, 11.24.

**[2*R*-[2α,3α(*S**)]]-[2-[[2-[1,1-Difluoro-2-oxo-2-(1-pyrrolidinyl)ethyl]tetrahydro-5-oxo-3-furanyl]amino]-1-methyl-2-oxoethyl]carbamic Acid, 1,1-Dimethylethyl Ester (18).** To a solution of the β-lactam alcohol **17** (158 mg, 0.637 mmol) and triethylamine (0.18 mL, 1.29 mmol) in anhydrous $CH_2Cl_2$ (4 mL) at 23 °C was added *N*-(*tert*-butoxycarbonyl)-L-alanine *N*-hydroxysuccinimide ester (200 mg, 0.698 mmol). The mixture was stirred at 23 °C for 18 h and then concentrated to leave an oil. This was chromatographed on silica gel eluting with 3:1 EtOAc/hexane as eluant. Fractions containing only **18** yielded an oil, 175 mg (66%): $[\alpha]^{20}_D$ −45.9° (*c* 3.50, $CH_2Cl_2$); $\nu_{max}$ 3428, 3324, 1802, 1693, 1650 $cm^{-1}$; $^1H$ NMR δ 1.28 (d, 3 H, *J* = 7.1 Hz, NCH*Me*), 1.39 (s, 9 H, *t*-Bu), 1.81–1.97 (m, 4 H, 2 × C*H*$_2$CH$_2$N), 2.58 (dd, 1 H, *J* = 7.8, 18.2 Hz, CHCO$_2$), 2.87 (dd, 1 H, *J* = 9.7, 18.2 Hz, CHCO$_2$), 3.50 (envelope. 2 H, 2 × CH$_2$C*H*N), 3.68 (envelope, 2 H, 2 × CH$_2$C*H*N), 4.14 (m, 1 H, NC*H*Me), 4.97 (m, 1 H, CHCF$_2$), 5.20 (br d, 1 H, *J* = 7.8 Hz, BOCNH), 5.27 (m, 1 H, overlapped, C*H*CH$_2$CO), 7.46 (br d, 1 H, *J* = 8.8 Hz, NH); $^{13}C$

NMR δ 18.3, 23.1, 26.4, 28.3, 33.7, 44.9, 46.9 (t, $J$ = 6 Hz), 48.0, 49.9, 78.4 (t, $J$ = 27 Hz), 114.6 (t, $J$ = 258 Hz), 155.3, 160.4 (t, $J$ = 28 Hz), 172.7, 172.9; MS (FAB) $m/z$ 420 ($MH^+$, 40), 364 (85), 320 (100), 249 (32); HRMS (FAB) calcd for $C_{18}H_{28}F_2N_3O_6$ ($MH^+$) 420.1947, found 420.1966.

**(2*R*-*cis*)-*N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-*N*-[2-[1,1-difluoro-2-oxo-2-(1-pyrrolidinyl)ethyl]tetrahydro-5-oxo-3-furanyl]-L-alaninimide (19).** To a solution of the lactone 18 (260 mg, 0.620 mmol) in $CH_2Cl_2$ (4 mL) cooled in an ice bath was slowly added TFA (4 mL). The resulting mixture was stirred for 2 h at 0 °C at which point the solvents were evaporated to leave an oil. This was dissolved in anhydrous $CH_2Cl_2$ (5 mL), and the solution was cooled in an ice bath. Diisopropylethylamine (0.20 mL, 1.15 mmol) and BOC-L-valine *N*-hydroxysuccinimide ester (290 mg, 0.922 mmol) were added sequentially. After being stirred for 4 h at 23 °C, the mixture was diluted with EtOAc and washed with 1 N HCl. The aqueous wash was extracted with EtOAc. The combined EtOAc fractions were washed with saturated $NaHCO_3$, dried, and concentrated to leave an oil which was chromatographed on silica gel eluting with 4:1 EtOAc/hexane. Fractions containing only **19** yielded an oil, 221 mg (69%): $[\alpha]^{20}_D$ −47.8° (*c* 1.38, $CHCl_3$); $\nu_{max}$ 3416, 3326, 1800, 1702 (sh), 1695, 1656 $cm^{-1}$; $^1H$ NMR δ 0.89 (d, 3 H, $J$ = 6.8 Hz, CH*Me*), 0.94 (d, 3 H, $J$ = 6.8 Hz, NCH*Me*), 1.33 (d, 3 H, $J$ = 7.0 Hz, NCH*Me*), 1.43 (s, 9 H, *t*-Bu), 1.81–2.05 (m, 4 H, 2 × C$H_2$CH$_2$N), 2.12 (m, 1 H, C*H*Me$_2$), 2.65 (dd, 1 H, $J$ = 8.3, 18.1 Hz, CHCO$_2$), 2.87 (dd, 1 H, $J$ = 9.8, 18.1 Hz, CHCO$_2$), 3.53 (envelope, 2 H, 2 × CH$_2$C*H*N), 3.70 (envelope, 2 H, 2 × CH$_2$C*H*N), 3.96 (m, 1 H, NC*H*-i-Pr), 4.47 (m, 1 H, NC*H*Me), 4.99 (m, 1 H, CHCF$_2$), 5.10 (br d, 1 H, BOCNH), 5.33 (m, 1 H, C*H*CH$_2$), 6.79 (br d, 1 H, $J$ = 7.5 Hz, NH), 7.43 (d, 1 H, $J$ = 9.2 Hz, NH); $^{13}C$ NMR δ 17.8, 18.5, 19.3, 23.1, 26.4, 28.3, 31.2, 33.6, 45.0, 46.8 (t, $J$ = 6 Hz), 47.9, 48.4, 59.6, 78.4 (t, $J$ = 27 Hz), 79.6, 114.7 (t, $J$ = 258 Hz), 155.9, 160.3 (t, $J$ = 28 Hz), 171.6, 172.0, 173.1; MS (FAB) $m/z$ 519 ($MH^+$, 62), 463 (62), 419 (84), 320 (71), 249 (100); HRMS (FAB) calcd for $C_{27}H_{37}F_2N_4O_7$ ($MH^+$) 519.2630, found 519.2620.

**[*R*-(*R**,*S**)]-*N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-*N*-[3,3-difluoro-2-hydroxy-4-oxo-1-[2-oxo-2-(phenylmethoxy)ethyl]-4-(1-pyrrolidinyl)butyl]-L-alaninimide (20).** A solution of the lactone **19** in MeOH (1.5 mL) and THF (1.5 mL) was cooled in an ice bath at 0 °C, and aqueous 1.31 M LiOH solution (0.25 mL, 0.33 mmol) was added. The mixture was stirred at 0 °C for 1 h and then at 23 °C for 2 h until disappearance of **19** was complete as determined by TLC (silica gel/EtOAc eluant). After evaporation of the solvents, the residue was dried under vacuum for 18 h to afford a white solid. This was dissolved in anhydrous DMF (3 mL), and benzyl bromide (0.055 mL, 0.46 mmol) was added. After being stirred at 23 °C for 4.5 h, the solution was poured into water, and the resulting mixture was extracted with EtOAc (3×). The combined EtOAc extracts gave a pale yellow oil on drying and evaporation. This was chromatographed on silica gel eluting with 4:1 EtOAc/hexane to afford **20** as a clear oil, 135 mg (71%): $[\alpha]^{20}_D$ −23.8° (*c* 1.14, $CHCl_3$); $\nu_{max}$ 3423, 1728 (sh), 1708 (sh), 1649 $cm^{-1}$); $^1H$ NMR δ 0.88 (d, 3 H, $J$ = 6.8 Hz, CH*Me*), 0.93 (d, 3 H, $J$ = 6.8 Hz, NCH*Me*), 1.33 (d, 3 H, $J$ = 7.0 Hz, NCH*Me*), 1.42 (s, 9 H, *t*-Bu), 1.82–2.02 (m, 4 H, 2 × C$H_2$CH$_2$N), 2.09 (m, 1 H, C*H*Me$_2$), 2.75 (*ABX* m, 2 H, CH$_2$CO$_2$), 3.50 (m, 2 H, 2 × CH$_2$C*H*N), 3.68 (envelope, 2 H, 2 × CH$_2$C*H*N), 3.94 (m, 1 H, NC*H*-i-Pr), 4.34 (br d, 1 H, $J$ = 21 Hz, CHCF$_2$), 4.48 (m, 1 H, NC*H*Me), 4.76 (m, 1 H, C*H*CH$_2$), 5.09 (AB d, 2 × 1 H, $J$ = 12.2 Hz, PhC$H_2$), 5.20 (br d, 1 H, $J$ = 8.2 Hz, BOCNH), 6.69 (br d, 1 H, $J$ = 7.3 Hz, NH), 6.95 (br d, 1 H, $J$ = 8.6 Hz, NH), 7.33 (s, 5 H, Ph); $^{13}C$ NMR δ 17.7, 18.6, 19.2, 23.2, 26.3, 28.3, 31.3, 36.7, 45.0, 46.5, 47.4, 48.8, 59.6, 66.5, 70.4 (dd, $J$ = 22, 29 Hz), 79.7, 115.5 (dd, $J$ = 258, 265 Hz), 128.2, 128.3, 128.4, 128.5, 135.5, 155.9, 161.9 (t, $J$ = 29 Hz), 170.6, 171.4, 171.7; MS (FAB) $m/z$ 627 ($MH^+$, 59), 571 (25), 553 (18), 527 (26), 509 (20), 428 (16), 357 (100), 320 (16), 267 (33), 249 (17); HRMS (FAB) calcd for $C_{30}H_{45}F_2N_4O_8$ ($MH^+$) 627.3208, found 627.3151.

**(*S*)-*N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-*N*-[3,3-difluoro-2,4-dioxo-1-[2-oxo-2-(phenylmethoxy)ethyl]-4-(1-pyrrolidinyl)butyl]-L-alaninimide (21).** To a solution of the γ-hydroxy ester **20** (129 mg, 0.206 mmol) in anhydrous $CH_2Cl_2$ (5 mL) at 23 °C was added the Dess–Martin reagent (1,1,1-triacetoxy-1,1-dihydro-1,2-benzidoxol-3(1*H*)-one) (320 mg, 0.75 mmol). The resulting heterogeneous mixture was stirred at 23 °C for 5 h and was then quenched by addition of EtOAc and a solution of sodium thiosulfate (1.2 g) in saturated $NaHCO_3$ solution (10 mL). After the mixture was stirred for about 15 min when all solids had dissolved, the aqueous layer was separated and extracted with EtOAc. The combined EtOAc layers were dried and evaporated to leave **21** as a clear oil (126 mg, 98%): $^1H$ NMR δ 0.87 (d, 3 H, $J$ = 6.8 Hz, CH*Me*), 0.93 (d, 3 H, $J$ = 6.8 Hz, NCH*Me*), 1.33 (d, 3 H, $J$ = 7.0 Hz, NCH*Me*), 1.42 (s, 9 H, *t*-Bu), 1.81–2.00 (m, 4 H, 2 × C$H_2$CH$_2$N), 2.10 (m, 1 H, C*H*Me$_2$), 2.97 (*ABX* m, 2 H, CH$_2$CO$_2$), 3.47 (envelope, 2 H, 2 × CH$_2$C*H*N), 3.62 (m, 2 H, 2 × CH$_2$C*H*N), 3.95 (m, 1 H, NC*H*-i-Pr), 4.52 (m, 1 H, NC*H*Me), 5.09 (AB d, 2 × 1 H, $J$ = 12.2 Hz, PhC$H_2$), 5.15–5.28 (m, 2 H, C*H*CH$_2$, BOCNH), 6.82 (br d, 1 H, $J$ = 7.4 Hz, NH), 7.30–7.41 (m, 6 H, Ph, NH); MS (FAB) $m/z$ ($MH^+$, 7), 569 (8), 525 (40), 355 (77), 147 (100); HRMS (FAB) calcd for $C_{30}H_{43}F_2N_4O_8$ ($MH^+$) 625.3051, found 625.3068.

Having a high degree of purity by $^1H$ NMR, the material was used immediately in the next step.

**(*S*)-*N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-*N*-[1-(carboxymethyl)-3,3-difluoro-2,4-dioxo-4-(1-pyrrolidinyl)-butyl]-L-alaninimide (1).** To a solution of **21** (124 mg, 0.198 mmol) in EtOH (25 mL) was added 10% Pd on charcoal. The mixture was hydrogenated at 3 atm of pressure for 5 h using a Parr shaker. After removal of the catalyst by filtration through Celite, the solvent was evaporated. The residue was chromatographed on silica gel using 1:5:94 AcOH/MeOH/$CHCl_3$ as eluant. Fractions highly enriched in **1** yielded a clear oil, 69 mg (65%): $\nu_{max}$ 3422, 1812, 1684, 1649 $cm^{-1}$; $^1H$ NMR δ 0.88 (d, 3 H, $J$ = 6.9 Hz, CH*Me*), 0.94 (d, 3 H, $J$ = 7.2 Hz, NCH*Me*), 1.34 (d, 1.5 H, overlapped, $J$ = 7.0 Hz, NCH*Me*), 1.36 (d, 1.5 H, overlapped, $J$ = 7.0 Hz, NCH*Me*), 1.41 (s, 9 H, *t*-Bu), 1.82–2.10 (m, 4 H, 2 × C$H_2$CH$_2$N), 2.12 (m, 1 H, C*H*Me$_2$), 2.60 (dd, 0.5 H, overlapped, $J$ = 8.8, 17.5 Hz, CHCO$_2$), 2.64 (dd, 0.5 H, overlapped, $J$ = 8.4, 17.5 Hz, CHCO$_2$), 2.99 (dd, 0.5 H, overlapped, $J$ = 8.5, 17.5 Hz, CHCO$_2$), 3.02 (dd, 0.5 H, overlapped, $J$ = 8.7, 17.5 Hz, CHCO$_2$), 3.53 (m, 2 H, 2 × CH$_2$C*H*N), 3.70 (envelope, 2 H, 2 × CH$_2$C*H*N), 3.96 (m, 1 H, NC*H*-i-Pr), 4.56 (m, 1 H, NC*H*Me), 5.08 (m, 1 H, CHCF$_2$), 5.32 (m, 1 H, BOCNH), 7.03 (br d, 0.5 H, $J$ = 7.2 Hz, NH), 7.12 (br d, 0.5 H, $J$ = 7.0 Hz, NH), 7.38 (d, 1 H, $J$ = 8.3 Hz, NH); $^{13}C$ NMR ($CDCl_3$) δ 17.8, 18.3, 19.2, 23.1, 26.3, 28.2, (31.0, 31.1), (34.0, 34.3), 46.7, 47.0, 47.9, (48.6, 48.9), 59.7, (79.9, 80.0), 104.0 (br), 110.3 (t, $J$ = 264 Hz), (156.0, 156.1), 161.2 (t, $J$ = 28 Hz), (171.2, 171.3), (172.0, 172.1), (172.3, 172.4); MS (FAB) $m/z$ 535 ($MH^+$, 59), 479 (34), 435 (93), 336 (23), 265 (100); HRMS (FAB) calcd for $C_{23}H_{37}F_2N_4O_8$ ($MH^+$) 535.2581, found 535.2597.

Other fractions containing **1** gave a clear oil (33 mg) contaminated with benzoic acid which was presumed to arise from reduction of a small amount of 2-iodobenzoic acid carried through from the Dess–Martin oxidation. The combined samples of **1** were again chromatographed on silica gel but this time 5/95 MeOH/$CHCl_3$ was used as eluant. Clean fractions containing **1** provided a clear oil (60 mg, 57%): $[\alpha]^{20}_D$ −26.4° (*c* 3.0, $CHCl_3$). The $^1H$ and $^{13}C$ NMR spectra of the sample indicated epimerization α to the ketone carbonyl had occurred (approximately 50%).[25]

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**Supplementary Material Available:** $^1H$ NMR and $^{13}C$ NMR spectra for most new compounds (41 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.