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SYNTHESIS OF *N*-BUTYL SIDE CHAIN HYDROXYLATED METABOLITES OF ROXIFIBAN, A PLATELET GLYCOPROTEIN IIB/IIIA RECEPTOR ANTAGONIST

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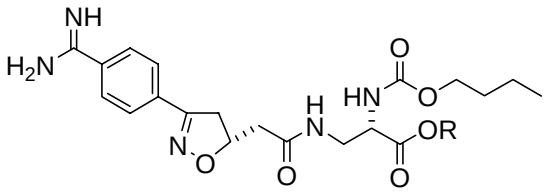
Abstract – Syntheses of three *n*-butyl side chain hydroxylated metabolites of Roxifiban (**5**, **6a** and **6b**) are reported. Initial use of benzyl as hydroxyl protecting group gave poor yield during its removal by catalytic hydrogenation, due to complication from *N-O* cleavage of the isoxazoline. This problem was eliminated by the use of TBDMS as the hydroxyl protecting group. The chemical structures of these metabolites as well as the intermediates have been fully characterized.

INTRODUCTION

Roxifiban (**1**) is a potent and selective antagonist of the platelet glycoprotein IIb/IIIa receptor.[1,2] Since roxifiban is an ester prodrug, it requires *in vivo* hydrolysis to the active XV459 (**2**). In fact, it has been shown that **2** was produced rapidly from **1** in the presence of liver microsomes, liver slices and intestinal segments.[3] Further studies have led to isolation of various hydroxylated metabolites (**3** – **7**).[3] Synthesis of *cis*- and *trans*-isomers of the isoxazoline ring-hydroxylated metabolites (**3a**) and (**3b**) has been recently reported.[4] The comparison of these synthetic standards with the isolated metabolite established the *trans* configuration for the hydroxylated metabolite. In this paper, we wish to report the first synthesis of three hydroxylated metabolites which are on the *n*-butyl side chain (i.e., **5**, **6a** and **6b**). The availability of these synthetic standards facilitated the structural determination and established the absolute configuration of the isolated metabolites unambiguously.[5]



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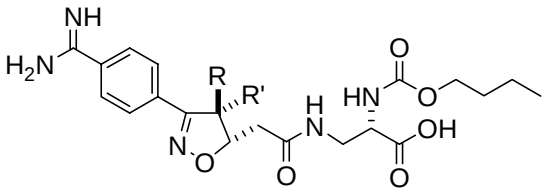
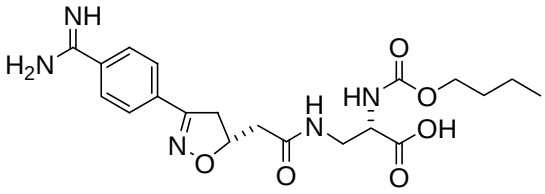
2, R = H



3a, R = OH, R' = H
3b, R = H, R' = OH



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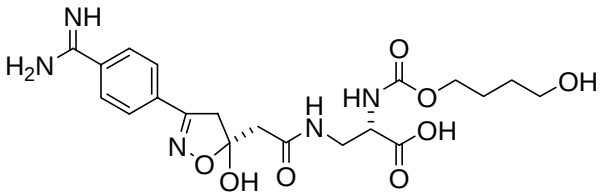
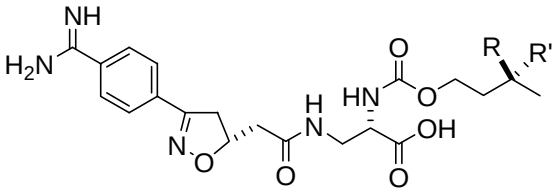
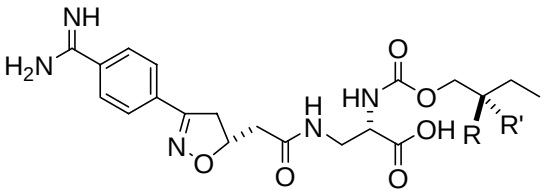


5



6a, R = OH, R' = H
6b, R = H, R' = OH



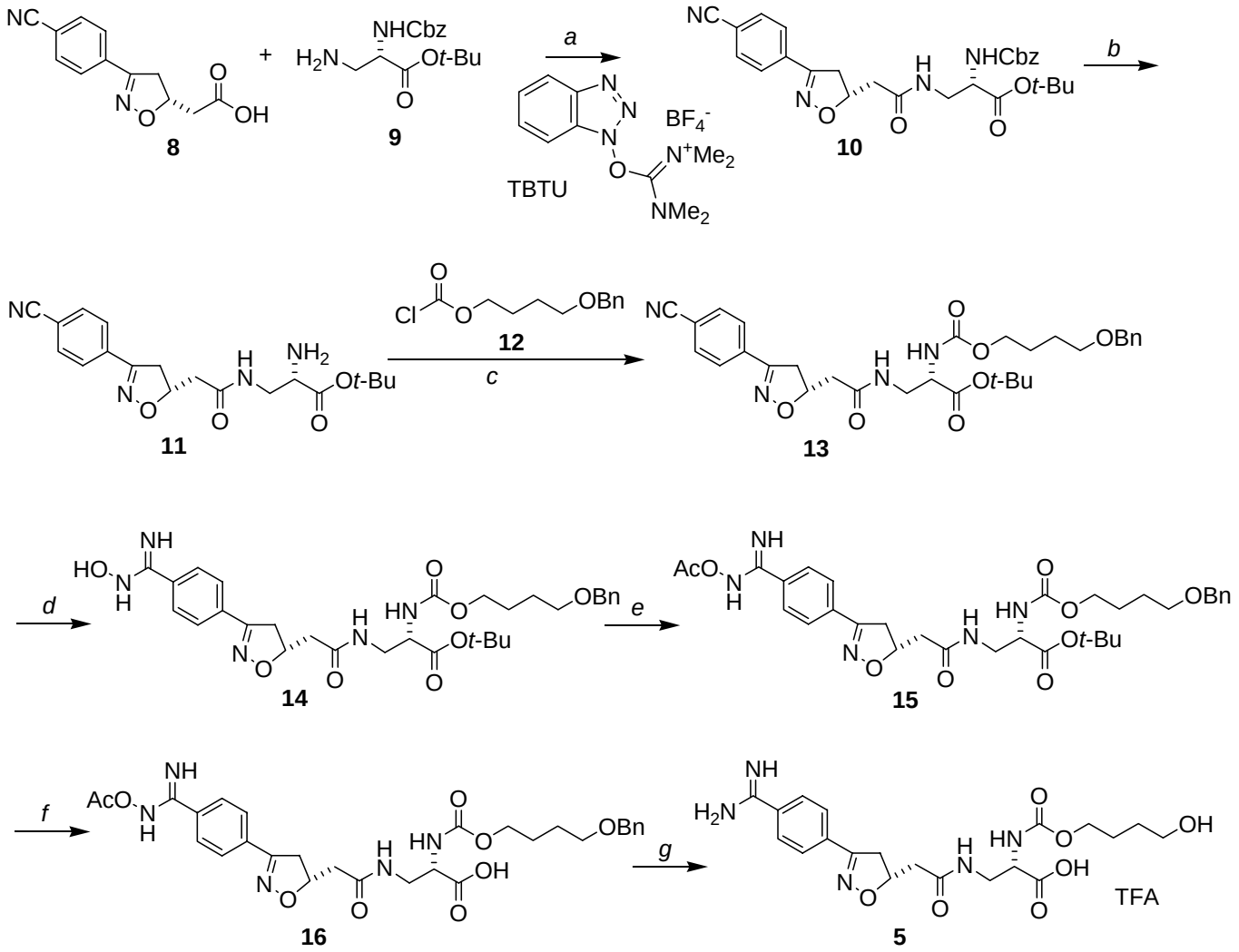
7a, R = OH, R' = H
7b, R = H, R' = OH

RESULTS AND DISCUSSION

The presence of an additional hydroxyl moiety relative to **2** adds complexity to the synthetic strategy and the need to select a hydroxyl protecting group, which ideally can be readily removed towards the end of the synthesis. We first studied the synthesis of *n*-butyl terminal hydroxylated derivative (**5**) because it has one less chiral center. We chose benzyl as the hydroxyl protecting group[6] because we envisioned that in the last step of the synthesis, both the hydroxyl and amidinyl moieties will be unveiled *via* catalytic hydrogenation from the protected precursor (see below).

Commencing from the acid (**8**),[7] activation with TBTU, followed by addition of the amine (**9)**,[8] furnished the amide (**10**) in 88% yield (Scheme 1). Removal of the CBZ moiety was effected by 20% $Pd(OH)_2$ and cyclohexadiene in MeOH heated to reflux and gave **11** in 55% yield. The amine was then coupled with the chloroformate (**12**), which was derived from the reaction of 4-benzyloxy-1-butanol with triphosgene, to give **13** in 81% yield. After reaction of **13** with hydroxylamine, the resulting **14** was treated with acetic anhydride to furnish **15** in 68% yield (two steps). The *tert*-butyl ester was hydrolyzed to the acid (**16**) with TFA in CH_2Cl_2 in 85% yield. Both of the *N*-acetoxy and *O*-benzyl bonds were cleaved under catalytic hydrogenation at room temperature with 5% Pd/C in acetic acid at 5 psi to afford **5** in 40% yield after purification by prep HPLC.

Scheme 1: Synthesis of Terminal Hydroxylbutyl Metabolite (5)[a]

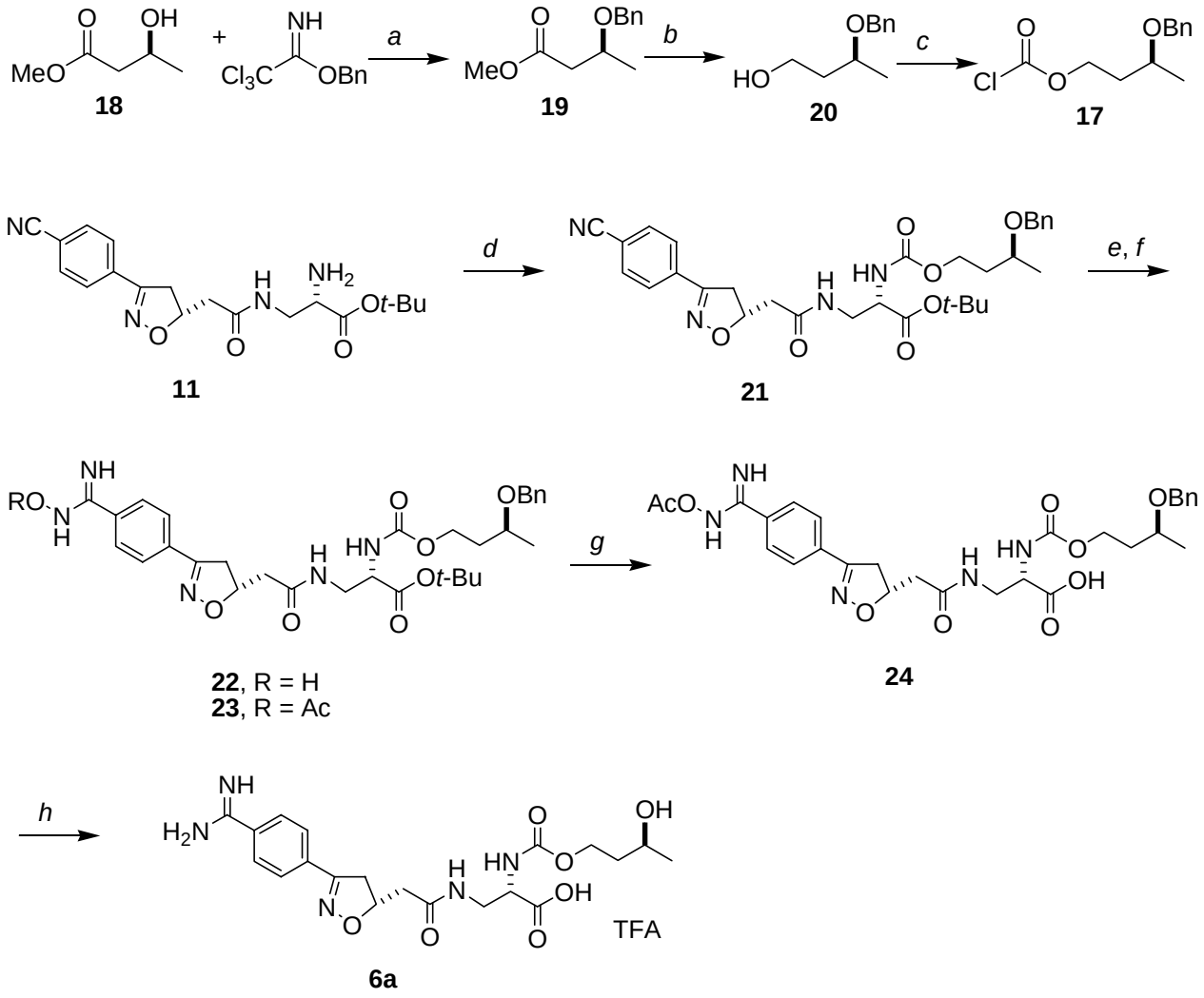


[a] Reagents: *a*, TBTU, Et_3N, DMF, rt, 88%; *b*, cyclohexadiene, $Pd(OH)_2$, MeOH, reflux, 55%; *c*, Et_3N, THF, rt, 81%; *d*, NH_2OH HCl, Et_3N, MeOH, reflux; *e*, Ac_2O, pyridine, CH_2Cl_2, rt, 68% (two steps); *f*, TFA, CH_2Cl_2, 85%; *g*, 5% Pd/C, H_2, 5 psi, HOAc, 40%.

The above synthetic scheme was then extended to synthesis of **6a** (Scheme 2). The requisite, novel chloroformate (**17**) was prepared in three steps from methyl (*S*)-3-hydroxybutyrate (**18**). *O*-Benzylation of **18** provided the ester (**19**),[9] which was reduced with LAH to give alcohol (**20**). This in turn was treated with triphosgene in the presence of Et_3N in THF, furnishing the chloroformate (**17)** in 80% yield. With the benzyl-protected chloroformate in hand, condensation with the amine (**11)** gave crude carbamate (**21**) in quantitative yield. The aforementioned two-step protocol (i.e., reaction with hydroxylamine, followed by addition of acetic anhydride) converted **21** to **23** *via* intermediate (**22**) in 62% overall yield. The ester hydrolysis of **23** was performed under standard conditions (TFA/CH_2Cl_2, rt) and afforded the

corresponding acid (**24**) in high yield. The final conversion of **24** to **6a** was investigated under a variety of catalytic hydrogenation conditions, due to complications resulting from competitive *N*-*O* cleavage of the isoxazoline and subsequent imine reduction. We also observed these side reactions during the synthesis of metabolite (**5**), but the side products were isolated unsizable quantity. The differences in product purity profiles may be attributed to the subtle steric hindrance of the secondary benzyl ether *vs.* the primary benzyl ether. Even under the optimal conditions (5% Pd/C in HOAc, 5 psi of H_2, rt), the product (**6a**) was obtained in 14% after purification by prep HPLC.

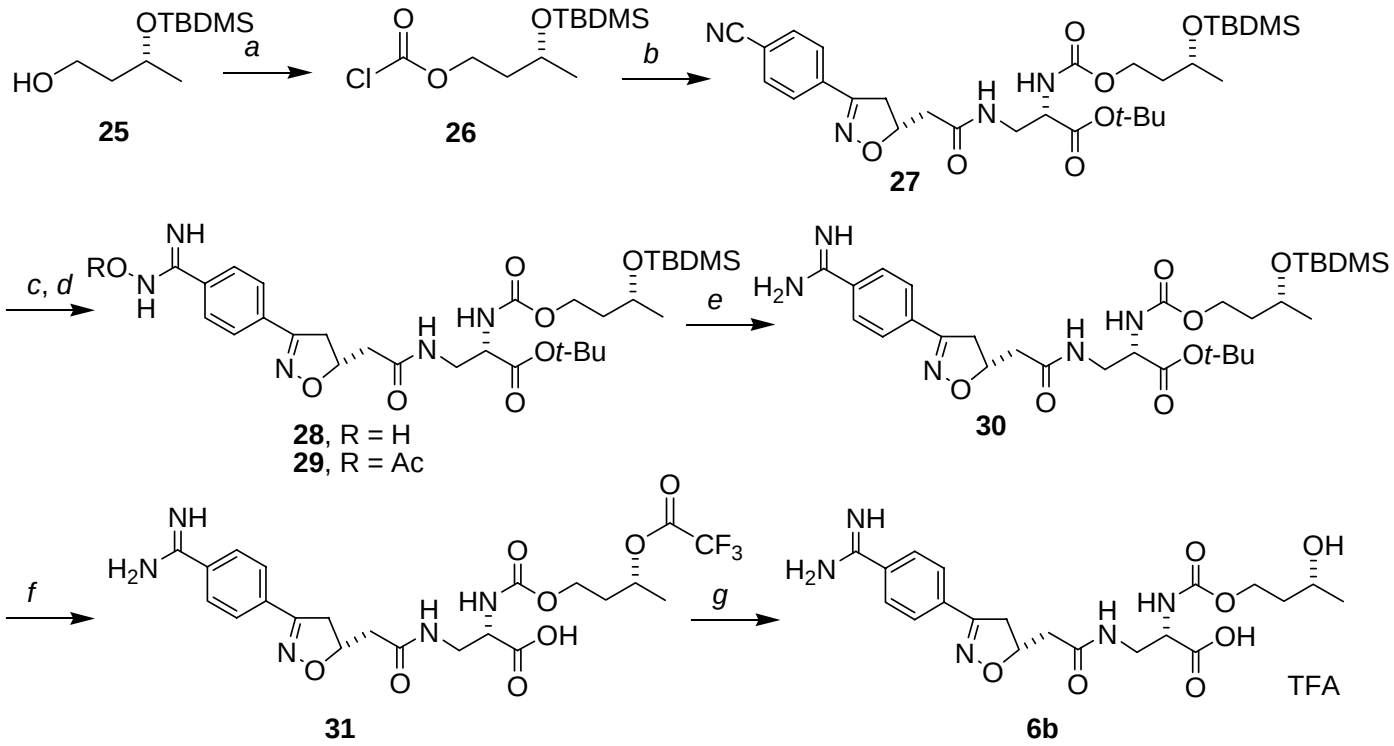
Scheme 2: Synthesis of Metabolite (6a) Using *O*-Benzyl Protecting Group[a]



[a] Reagents: *a*, cyclohexane, CH_2Cl_2, triflic acid; *b*, LAH, THF, 82%; *c*, triphosgene, Et_3N, THF, 80%; *d*, **17**, Et_3N, THF, 100%; *e*, NH_2OH HCl, Et_3N, MeOH, reflux; *f*, Ac_2O, pyridine, CH_2Cl_2, rt, 62% (two steps); *g*, TFA, CH_2Cl_2, 100%; *h*, 5% Pd/C, H_2, 5 psi, HOAc, 14%.

Because of very poor yield of *O*-debenzylation, TBDMS was chosen as an alternate hydroxyl-protecting group for the synthesis of **6b** (Scheme 3). We expected that the deprotection to the alcohol, under mild acidic conditions, would be compatible with the functionality present in **6b**. Thus, reaction of the alcohol (**25**) with triphosgene in the presence of Et_3N in THF furnished the chloroformate (**26**) in 50% yield after purification by flash column chromatography. As expected, subsequent reaction with the amine (**11**) produced the carbamate (**27**) in 74% yield. Treatment of **27** with hydroxylamine hydrochloride in the presence of Et_3N in refluxing MeOH gave **28** in 93% yield. After *O*-acetylation with acetic anhydride, the resulting (**29**) was subjected to hydrogenation (5% Pd/C with 20 psi of H_2 at rt) and provided **30** in quantitative yield. It was our plan that acid hydrolysis of **30** with TFA should give **6b**. But to our surprise, the *O*-trifluoroacetyl derivative (**31**) was isolated in 88% yield instead. We were gratified to find that by simply stirring a solution of **31** in water at room temperature, the desired **6b** was isolated in 95% yield after lyophilization. The overall yield for the synthesis of **6b** employing TBDMS as the protecting group was 21% for 7 steps.

Scheme 3: Synthesis of Metabolite (6b) Using *O*-TBDMS Protecting Group[a]



[a] Reagents: *a*, triphosgene, Et_3N, THF, 50%; *b*, **11**, Et_3N, THF, 74%; *c*, NH_2OH HCl, Et_3N, MeOH reflux, 93%; *d*, Ac_2O, pyridine, CH_2Cl_2, rt; *e*, 5% Pd/C, H_2, HOAc, 100% (two steps); *f*, TFA/CH_2Cl_2, rt, 88%; *g*, H_2O, rt, 95%.

In conclusion, we have achieved the first synthesis of roxifiban metabolites (**5**, **6a**, and **6b**). Our initial use of an *O*-benzyl protecting group was complicated by isoxazoline ring cleavage under catalytic hydrogenation and resulted in poor yield of the desired product (**6a)**. This problem was overcome by switching to the *O*-TBDMS protecting group. Removal by acid hydrolysis was facile and furnished **6b** in greatly improved yield. Comparison of the synthetic standards with the isolated metabolites demonstrated that both enantiomers (**6a**) and (**6b**) are present with the (*S*)-enantiomer (**6a**) predominating.[10]

EXPERIMENTAL

Starting materials, reagents, and solvents were obtained from commercial sources and used as received. All reactions were carried out with continuous stirring under an atmosphere of dry nitrogen. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on either Varian VXRS-300 or VXRS-400 spectrometers using tetramethylsilane as an internal standard. Melting points were uncorrected. TLC was performed on E. Merck 15719 silica gel 60 (230-400 mesh). Elemental analyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ.

***tert*-Butyl *N*-(benzyloxycarbonyl)-3-({[(5*R*)-3-(4-cyanophenyl)-4,5-dihydro-5-isoxazolyl]-acetyl}amino)-L-alaninate (10).** To a solution of **8** (7.15 g, 31 mmol), **9** (11 g, 37.4 mmol) and TBTU (12 g, 37.4 mmol) in 150 mL of DMF was added Et_3N (10.4 mL, 74.6 mmol). After stirring at rt for 5 h, the reaction solution was treated with water (150 mL) and EtOAc (150 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 100 mL, 1 X 50 mL). The combined organic layers were washed with water (2 x 100 mL), 5% $NaHCO_3$ (2 x 100 mL), brine, dried (Na_2SO_4), filtered and evaporated. Chromatography (silica gel, 40-80% EtOAc/hexane) gave **10** (13.75 g, 88% yield) as an off-white, crystalline solid. **10:** mp 83-84 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.36-7.33 (m, 5H), 6.30 (br, 1H), 5.68 (br, 1H), 5.12-5.06 (m, 3H), 4.35 (br, 1H), 3.67-3.41 (m, 3H), 3.24-3,15 (m, 1H), 2.68-2.62 (m, 1H), 2.52-2.45 (m, 1H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.5, 169.0, 155.8, 136.2, 133.7, 132.5, 128.6, 128.3, 128.1, 127.2, 118.2, 113.6, 83.3, 78.6, 67.2, 54.6, 42.2, 41.4, 39.4, 27.9; MS (AP^{+}) *m/z* 507.1 (M + H, 100); IR (KBr) 3354, 2978, 2228, 1723, 1671, 1589, 1527, 1368, 1351, 1251, 1156 cm^{-1}. Anal. Calcd for $C_{27}H_{30}N_4O_6$: C, 63.85; H, 5.98; N, 10.90. Found: C, 64.02, H, 5.97, N, 11.06.

***tert*-Butyl 3-({[(5*R*)-3-(4-cyanophenyl)-4,5-dihydro-5-isoxazolyl]acetyl}amino)-L-alaninate (11).** A mixture of **10** (1 g, 2 mmol), 20% palladium hydroxide (0.2 g) and 1,4-cyclohexadiene (13

mL) in 40 mL of MeOH was heated to reflux for 6 h and stirred at rt overnight. The catalyst was removed by filtration through a pad of Celite. The filter cake was washed with MeOH. The solvent in the filtrate was evaporated to dryness. Chromatography (silica gel, 1-5% MeOH/CH_2Cl_2) gave **11** (0.51 g, 55% yield) as a light yellow solid. **11:** mp 64-65 ^oC; ^1H NMR ($CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 7.3 Hz, 2H), 6.39 (br, 1H), 5.19-5.14 (m, 1H), 3.69-3.61 (m, 1H), 3.57-3.44 (m, 2H), 3.32-3.21 (m 2H), 2.75-2.56 (m, 2H), 1.62 (br, 2H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.86, 168.98, 155.77, 133.69, 132.50, 127.16, 118.24, 113.58, 82.08, 78.73, 54.33, 42.71, 41.59, 39.40, 28.00; MS (ES^+) *m/z* 372.9 (M + H, 100); IR (KBr) 3379, 2978, 2933, 2228, 1728, 1668, 1540, 1368, 1157, 843 cm^{-1}; Anal. Calcd for $C_{19}H_{24}N_4O_4$: C, 61.28; H, 6.50; N, 15.04. Found: C, 60.96; H, 6.36; N, 14.80.

4-Benzyloxybutyl chlorocarbonate (12) Analogous to **26**, **12** was prepared in 66% yield as a clear liquid. ^1H NMR ($CDCl_3$) δ 7.38-7.28 (m, 5H), 4.50 (s, 2H), 4.35 (t, J = 6.4 Hz, 2H), 3.51 (t, J = 6.1 Hz, 2H), 1.90-1.81 (m, 2H), 1.75-1.66 (m, 2H); MS (AP^+) *m/z* 239.2 (M + H for the methyl carbonate derivative, $C_{13}H_{18}O_4$, MW 238).

***tert*-Butyl *N*-(4-benzyloxybutoxycarbonyl)-3-({[(5*R*)-3-(4-cyanophenyl)-4,5-dihydro-5-isoxazolyl]acetyl}amino)-L-alaninate (13).** To a solution of **11** (1.84 g, 4.94 mmol) in 25 mL of THF was added a solution of **12** (1.80 g, 4.96 mmol) in 5 mL of THF, followed by Et_3N (0.8 g, 7.9 mmol) at rt. After stirring for 15 min, the reaction was complete. The mixture was treated with EtOAc (100 mL) and water (30 mL). After separation of layers, the organic layer was washed with pH 4 buffer solution, brine, dried (Na_2SO_4), and evaporated to dryness. Chromatography (silica gel, 0-60% EtOAc/hexane) gave **13** (2.32 g, 81% yield) as a white solid. **13:** mp 58-59 ^oC; ^1H NMR ($CDCl_3$) δ 7.77-7.67 (m, 4H), 7.34-7.33 (m, 5H), 6.36 (br, 1H), 5.61 (br, 1H), 5.14 (m, 1H), 4.50 (s, 2H), 4.34 (m, 1H), 4.16-4.11 (m, 3H), 3.66-3.45 (m, 4H), 3.21 (dd, J = 16.5, 7.4 Hz, 1H), 2.70 (dd, J = 14.3, 5.5 Hz, 1H), 2.55 (dd, J = 14.9, 5.7 Hz, 1H), 1.70 (br s, 4H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.44, 169.08, 155.78, 138.50, 133.66, 132.47, 128.38, 127.59, 127.20, 118.24, 113.59, 83.26, 78.59, 72.95, 69.78, 65.37, 60.37, 54.51, 41.50, 39.44, 27.94, 26.20, 25.87; MS (ES^+) *m/z* 579.4 (M + H, 30); IR (KBr) 3354, 3064, 2937, 2867, 2228, 1721, 1673, 1525, 1368, 1251, 1156, 1072 cm^{-1}; Anal. Calcd for $C_{31}H_{38}N_4O_7$: C, 64.35; H, 6.62; N, 9.68. Found: C, 64.13; H, 6.57; N, 9.59.

***tert*-Butyl *N*-(4-benzyloxybutoxycarbonyl)-3-{[((5*R*)-3-{4-[(hydroxyamino)(imino)-methyl]phenyl}-4,5-dihydro-5- isoxazolyl)acetyl]amino}-L-alaninate (14).** To a solution of **13** (0.48 g, 0.83 mmol) in 10 mL of MeOH was added hydroxylamine hydrochloride (0.12 g, 1.66 mmol) and Et_3N (0.23 mL, 1.66 mmol) at rt. The reaction mixture was then heated to reflux for 4

h and stirred at rt for 20 h. The solvent in the mixture was evaporated. The remaining residue was triturated with water. The water in the mixture was decanted. The treatment was repeated two more times. The residue was dried in a desiccator to give **14** in quantitative yield, which was used for the subsequent reaction without purification. **14:** ^{1}H NMR ($CDCl_3$) δ 7.62 (s, 4H), 7.32 (m, 5H), 6.66 (m, 1H), 5.80 (d, J = 7.7 Hz, 1H), 5.08-5.01 (m, 1H), 4.95 (br s, 2H), 4.49 (s, 2H), 4.36 (m, 1H), 4.07 (m, 2H), 3.64 (m, 1H), 3.50-3.38 (m, 3H), 2.65 (dd, J = 14.7, 6.6 Hz, 1H), 2.48 (dd, J = 14.9, 6.4 Hz, 1H), 1.68 (br s, 4H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.95, 169.36, 156.48, 152.08, 138.48, 134.06, 130.68, 128.37, 127.63, 127.55, 126.93, 126.09, 83.16, 77.98, 72.92, 69.81, 65.33, 54.61, 41.59, 39.90, 27.95, 26.15, 25.84; MS (ES^+) *m/z* 612.2 (M + H, 100).

***tert*-Butyl 3-{[((5*R*)-3-{4-[(acetyloxyamino)(imino)methyl]phenyl}-4,5-dihydro-5-isoxazolyl)acetyl]amino}-*N*-(4-benzyloxybutoxycarbonyl)-L-alaninate (15).** A solution of **14** (1.06 g, 1.73 mmol), acetic anhydride (0.23 g, 2.25 mmol) and pyridine (0.2 g, 2.53 mmol) in 30 mL of CH_2Cl_2 was stirred at rt for 2 h. The reaction solution was washed with water (2 X) and brine (1 X), dried (Na_2SO_4), and evaporated to dryness. Chromatography (silica gel, 0-4% MeOH/CH_2Cl_2) gave **15** (0.77 g, 68% yield) as a white solid. **15:** ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.37-7.29 (m 5H), 6.40 (br, 1H), 5.62 (d, J = 6.6 Hz, 1H), 5.14 (br, 2H), 5.09-5.06 (m, 1H), 4.49 (s, 2H), 4.32 (br, 1H), 4.09-4.05 (m, 2H), 3.61-3.59 (m, 2H), 3.54-3.44 (m, 3H), 3.14 (dd, J = 16.9, 7.4 Hz, 1H), 2.68 (dd, J = 14.8, 6.4 Hz, 1H), 2.54 (dd, J = 14.9, 6.1 Hz, 1H), 2.25 (s, 3H), 1.68 (br, 4H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.73, 169.16, 168.73, 156.35, 155.16, 138.50, 132.62, 131.82, 128.38, 126.62, 127.56, 126.99, 83.15, 78.09, 72.93, 69.82, 65.30, 54.59, 42.00, 41.64, 39.85, 27.95, 26.17, 25.84, 19.87; MS (ES^+) *m/z* 676.2 (M + Na, 100).

3-{[((5*R*)-3-{4-[(Acetyloxyamino)(imino)methyl]phenyl}-4,5-dihydro-5-isoxazolyl)acetyl]amino}-*N*-(4-benzyloxybutoxycarbonyl)-L-alanine (16). A solution of **15** (0.6 g, 0.92 mmol) in 12 mL of CH_2Cl_2 and 6 mL of TFA was stirred at rt for 2 h. The solvent and TFA were evaporated to dryness. The residue was dissolved in CH_2Cl_2, neutralized with saturated $NaHCO_3$, and then adjusted to pH 4 with HOAc. The resulting precipitates were collected on a filter, washed with CH_2Cl_2 to give **16** (0.47 g, 85% yield) as a white solid. **16**: mp 143-144 ^{o}C; ^{1}H NMR (DMSO-d_6) δ 8.12 (m, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.37-7.22 (m, 5H), 6.89 (s, 2H), 5.02-4.96 (m 1H), 4.44 (s, 2H), 4.05 (m, 1H), 3.96 (m 2H), 3.56-3.13 (m, 8H), 2.53 (m, 1H), 2.44 (m, 1H), 1.60 (s, 3H), 1.59 (m, 4H); MS (ES^+) *m/z* 598.1 (M + H, 100).

3-{[((5*R*)-3-{4-[Amino(imino)methyl]phenyl}-4,5-dihydro-5-isoxazolyl)acetyl]amino}-*N*-

(4-hydroxybutoxycarbonyl)-L-alanine trifluoroacetate (5). A mixture of **16** (0.5 g, 0.84 mmol) and 5% Pd/C (0.25 g) in 150 mL of HOAc was hydrogenated at rt at 5 psi for 27.5 h. The catalyst was removed by filtration. The solvent in the filtrate was evaporated and the residue was purified by prep HPLC to give **5** (186 mg, 40% yield) as a white solid. **5:** mp 190-197 ^{o}C; ^{1}H NMR (DMSO-d_6) δ 9.37 (s, 2H), 9.29 (s, 2H), 8.12 (t, J = 5.8 Hz, 1H), 7.89-7.82 (m, 4H), 7.28 (d, J = 8.3 Hz, 1H), 6.54 (s, 1H), 5.07-5.01 (m, 1H), 4.40 (br, 1H), 4.11-4.05 (m, 1H), 3.98-3.92 (m, 2H), 3.58-3.51 (m, 2H), 3.31 (br, 2H), 3.27-3.17 (m, 2H), 2.58 (dd, J = 14.4, 6.3 Hz, 1H), 2.44 (dd, J = 14.4, 7.1 Hz, 1H), 1.58-1.52 (m, 2H), 1.49-1.40 (m, 2H) ; ^{13}C NMR (DMSO-d_6) δ 171.99, 169.23, 165.00, 156.19, 156.05, 134.27, 129.07, 128.59, 127.77, 78.60, 64.04, 60.25, 53.65, 40.53, 39.78, 38.83, 28.77, 25.35; ^{19}F NMR (DMSO-d_6) δ -73.00; MS (ES^{+}) *m/z* 450.4 (M + H, 100); HRMS (ESI) *m/z* calcd for $C_{20}H_{28}N_5O_7$ [(M + H)] 450.1989, found 450.1996; IR (KBr) 3317, 3104, 1694, 1667, 1541, 1204, 1190. 1135 cm^{-1}. HPLC purity: > 99%.

(3*S*)-3-Benzyloxy-1-butanol (20). To a solution of the ester (**19**)[9] (5.8 g, 28 mmol) in 115 mL of anhydrous THF was added 1 M lithium aluminum hydride (56 mL, 56 mmol) while the temperature maintained at < 0 ^{o}C during the addition. The mixture was stirred at ambient temperature overnight and treated with 15% NaOH (26 mL) at < 0 ^{o}C. After warming to rt, the inorganic salt was removed by filtration. The filtrate was evaporated. The residue was partitioned between EtOAc (150 mL) and water (50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), and evaporated. Chromatography (silica gel, 30-100% butyl chloride/hexane, then 15% EtOAc/hexane) gave **20** (4.1 g, 82% yield) as a colorless oil. **20:** ^{1}H NMR ($CDCl_3$) δ 7.36-7.28 (m, 5H), 4.65 (d, J = 11.4 Hz, 1H), 4.45 (d, J = 11.3 Hz, 1H), 3.83-3.74 (m, 3H), 2.48-2.45 (m, 1H), 1.81-1.75 (m, 2H), 1.26 (d, J = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.46, 128.47, 127.71, 74.61, 70.48, 60.88, 38.88, 19.36; MS (ES^{+}) *m/z* 181.0 (M + H, 100); $[\alpha]_D^{25}$ +48.9^{o} (*c* 0.772, MeOH); IR (KBr) 3406, 2968, 2931, 2872, 1453, 1375, 1140, 1093, 1053, 1028, 736, 697 cm^{-1}; Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.96;. Found: C, 73.68; H, 9.05.

(3*S*)-3-Benzyloxybutyl chlorocarbonate (17). Analogous to **26**, **17:** 6.8 g, 80% yield as a colorless liquid; ^{1}H NMR ($CDCl_3$) δ 7.38-7.26 (m, 5H), 4.62 (d, J = 11.7 Hz, 1H), 4.51-4.37 (m, 3H), 3.70-3.64 (m, 1H), 1.94-1.87 (m, 2H), 1.25 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 150.57, 138.38, 128.44, 127.75, 127.71, 70.86, 70.59, 69.23, 35.51, 19.53; $[\alpha]_D^{25}$ +73.9^{o} (*c* 1.990, $CHCl_3$); IR (KBr) 2972, 2931, 2869, 1778, 1496, 1454, 1377, 1342, 1240, 1164, 1065, 1028, 933, 833, 737, 698, 690 cm^{-1}; Anal. Calcd for $C_{12}H_{15}O_3Cl$: C, 59.39; H, 6.24; Cl, 14.61;. Found: C, 59.07; H, 5.98; Cl, 14.82.

***tert*-Butyl *N*-((3*S*)-3-benzyloxybutoxycarbonyl)-3-({[(5*R*)-3-(4-cyanophenyl)-4,5-dihydro-5-isoxazolyl]acetyl}amino)-L-alaninate. (21)** Analogous to **13**, **21:** ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.34-7.28 (m, 5H), 6.31 (br, 1H), 5.56 (m, 1H), 5.16-5.10 (m, 1H), 4.58 (d, J = 11.3 Hz, 1H), 4.53 (d, J = 11.4 Hz, 1H), 4.32 (m, 1H), 4.19 (t, J = 6.8 Hz, 2H), 3.71-3.63 (m, 2H), 3.56-3.44 (m, 2H), 3.20 (dd, J = 16.9, 7.7 Hz, 1H), 2.68 (dd, J = 14.7, 6.3 Hz, 1H), 2.53 (dd, J = 14.8, 6.4 Hz, 1H), 1.90-1.76 (m, 2H), 1.48 (s, 9H), 1.23 (d, J = 6.6 Hz, 3H); MS (ES^+) *m/z* 579.1 (M + H, 30); IR (KBr) 2230, 1732 cm^{-1}.

***tert*-Butyl 3-{[((5*R*)-3-{4-[(*Z*)-amino(hydroxyimino)methyl]phenyl}-4,5-dihydro-5-isoxazolyl)acetyl]amino}-*N*-((3*S*)-3-benzyloxybutoxycarbonyl)-L-alaninate (22).** Analogous to **14**, **22:** 1.9 g, 95% yield as an oil; ^{1}H NMR ($CDCl_3$) δ 7.63-7.56 (m, 4H), 7.33-7.24 (m, 5H), 6.62 (br, 1H), 5.78 (d, J = 7.3 Hz, 1H), 5.06-5.01 (m, 1H), 4.96 (s, 2H), 4.57 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 11.7 Hz, 1H), 4.36 (m, 1H), 4.19 (t, J = 6.4 Hz, 2H), 3.68-3.62 (m, 3H), 3.48-3.35 (m, 1H), 3.02 (dd, J = 14.9, 7.4 Hz, 1H), 2.63 (dd, J = 15.0, 6.6 Hz, 1H), 2.45 (dd, J = 15.0, 6.2 Hz, 1H), 1.90-1.76 (m, 2H), 1.48 (s, 9H), 1.21 (d, J = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.94, 169.37, 156.44, 152.06, 138.76, 134.04, 130.68, 128.35, 127.67, 127.50, 126.91, 126.09, 83.18, 77.97, 71.90, 70.49, 62.60, 54.64, 41.85, 41.58, 39.90, 36.06, 27.95, 19.69; MS (ES^+) *m/z* 612.2 (M + H, 80); IR (KBr) 3350, 2974, 2932, 1719, 1643, 1593, 1527, 1454, 1394, 1369, 1307, 1250, 1156, 1067, 844 cm^{-1}; Anal. Calcd for $C_{31}H_{41}N_5O_8$ 0.5 H_2O: C, 59.99; H, 6.82; N, 11.28;. Found: C, 60.02; H, 6.75; N, 10.92.

***tert*-Butyl 3-{[((5*R*)-3-{4-[(*Z*)-[(acetyloxy)imino](amino)methyl]phenyl}-4,5-dihydro-5-isoxazolyl)acetyl]amino}-*N*-((3*S*)-3-benzyloxybutoxycarbonyl)-L-alaninate (23).** Analogous to **15**, **23:** 1.3 g, 65% yield as a white foam; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.8 Hz, 2H) 7.64 (d, J = 8.4 Hz, 2H), 7.33-7.24 (m, 5H), 6.47 (m, 1H), 5.65 (d, J = 7.0 Hz, 1H), 5.21 (s, 2H), 5.10-5.05 (m, 1H), 4.57 (d, J = 11.7 Hz, 1H), 4.43 (d, J = 11.7 Hz, 1H), 4.32 (m, 1H), 4.18 (t, J = 6.6 Hz, 2H), 3.68-3.54 (m, 3H), 3.46 (dd, J = 16.9, 10.3 Hz, 1H), 3.13 (dd, J = 17.1, 7.5 Hz, 1H), 2.66 (dd, J = 14.6, 6.6 Hz, 1H), 2.51 (dd, J = 14.7, 6.3 Hz, 1H), 2.25 (s, 3H), 1.87-1.74 (m, 2H), 1.48 (s, 9H), 1.22 (d, J = 5.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.78, 169.19, 168.76, 156.58, 156.32, 155.25, 138.76, 132.63, 131.76, 128.36, 127.67, 127.52, 127.04, 126.93, 83.09, 78.09, 71.92, 70.49, 62.53, 54.68, 41.90, 41.62, 39.84, 36.05, 27.96, 19.87, 19.68; MS (ES^+) *m/z* 654.2 (M + H, 100); IR (KBr) 3341, 2974, 2932, 1721, 1638, 1529, 1404, 1368, 1228, 1156, 1067 cm^{-1}; Anal. Calcd for $C_{33}H_{43}N_5O_8$: C, 60.63; H, 6.63; N, 10.71; Found: C, 60.24; H, 6.58; N, 10.51.

3-{[((5*R*)-3-{4-[(*Z*)-[(Acetyloxy)imino](amino)methyl]phenyl}-4,5-dihydro-5-isoxazolyl)acetyl]amino}-*N*-((3*S*)-3-benzyloxybutoxycarbonyl)-L-alanine (24). Analogous to **16**, **24:** 2.1 g,

100% yield as an oil; ^{1}H NMR ($CDCl_3$) δ 7.57 (d, J = 7.7 Hz, 2H) 7.49 (d, J = 7.7 Hz, 2H), 7.31-7.21 (m, 5H), 6.16 (d, J = 6.6 Hz, 1H), 5.57 (br s, 2H), 5.01 (m, 1H), 4.54 (d, J = 11.7 Hz, 1H), 4.41 (d, J = 11.8 Hz, 1H), 4.34 (m, 1H), 4.16 (t, 2H), 3.63-3.59 (m, 3H), 3.34 (dd, J = 16.9, 10.3 Hz, 1H), 3.00 (m, 1H), 2.64 (dd, J = 15.1, 7.3, 1H), 2.50 (dd, J = 14.5, 5.7 Hz, 1H), 2.19 (s, 3H), 1.79 (m 2H), 1.19 (d, J = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.93, 173.29, 169.17, 156.56, 156.06, 138.60, 132.41, 131.49, 128.37, 127.72, 127.56, 127.18, 126.89, 78.10, 71.89, 70.43, 62.68, 60.43, 54.54, 41.27, 39.54, 35.90, 20.67, 19.74; MS (ES^+) *m/z* 598.1 (M + H, 100); Anal. Calcd for $C_{29}H_{35}N_5O_9$ 1.5 CH_3CO_2H: C, 55.09; H, 5.92; N, 10.04;. Found: C, 54.94. 54.92; H, 5.47, 5.65; N, 10.47, 10.35.

3-{[((5*R*)-3-{4-[Amino(imino)methyl]phenyl}-4,5-dihydro-5-isoxazolyl)acetyl]amino}-*N*-((3*S*)-3-hydroxybutoxycarbonyl)-L-alanine trifluoroacetate (6a). Analogous to **5**, **6a:** 177 mg, 14% yield as a white powder; mp 154-156 ^{o}C; ^{1}H NMR (DMSO-d_6) δ 12.75 (s, 1H), 9.37 (s, 2H), 9.24 (s, 2H), 8.12 (t, J = 5.9 Hz, 1H), 7.89-7.84 (m, 4H), 7.27 (d, J = 8.3 Hz, 1H), 5.07-4.99 (m, 1H), 4.47 (br s, 1H), 4.11-3.97 (m, 3H), 3.67 (m, 1H), 3.58-3.51 (m, 2H), 3.27-3.17 (m, 2H), 2.58 (dd, J = 14.4, 6.3 Hz, 1H), 2.44 (dd, J = 14.3, 7.2 Hz, 1H), 1.61-1.56 (m, 2H), 1.05 (d, J = 6.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 171.97, 169.22, 164.98, 156.19, 156.05, 134.27, 129.06, 128.59, 126.76, 78.60, 62.84, 61.67, 53.66, 40.52, 39.76, 38.83, 38.13, 23.73; ^{19}F NMR (DMSO-d_6) δ -73.02; MS (ES^+) *m/z* 449.9 (M + H, 100); HRMS (ESI) *m/z* calcd for $C_{20}H_{28}N_5O_7$ [(M + H)] 450.1989, found 450.1997; IR (KBr) 3318, 1670, 1540, 1206, 1136 cm^{-1}; Anal. Calcd for $C_{20}H_{27}N_5O_7$ 1.15 CF_3CO_2H: C, 46.14; H, 4.89; N, 12.07; F, 11.29; Found: C, 46.36; H, 4.72; N, 12.22; F, 11.65.

(3*R*)-3-*tert*-Butyl(dimethyl)silyloxybutyl chlorocarbonate (26). To a solution of triphosgene (2.08 g, 7 mmol) in 300 mL of THF was added a solution of **25** (4.29 g, 21 mmol) in 30 mL of THF at - 15 ^{o}C, followed by a solution of Et_3N in 10 mL of THF dropwise. During the addition, the reaction temperature was maintained at < 5 ^{o}C. After the addition was complete, the mixture was further stirred at 0 - 10 ^{o}C for 1.5 h. The resulting white solid (triethylammonium hydrogen chloride) was removed by filtration. The solvent in the filtrate was evaporated to give a colorless liquid. Chromatography (silica gel, 0-1% EtOAc/hexane) gave **26** (2.81 g, 50% yield) as a colorless liquid. **26:** ^{1}H NMR ($CDCl_3$) δ 4.36-4.22 (m, 2H), 3.94-3.84 (m, 1H), 1.86-1.63 (m, 2H), 1.11 (J = 6.2 Hz, 3H), 0.82 (s, 9H), 0.0 (s, 3H), -0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 150.22, 69.40, 64.69. 37.76, 25.77, 23.95, 17.97, -4.37. The MS sample was prepared by heating a solution 2 mg of **26** in 1 mL of MeOH for 5 min, producing its methyl carbonate derivative ($C_{12}H_{26}O_4Si$, MW 262); MS (AP^+) *m/z* 263.2 (M + H, 100); IR (neat) 2957, 2930, 2858, 1781,

1257, 1163, 1148, 1047, 1005, 836, 776 cm^{-1}. Anal. Calcd for $C_{11}H_{23}O_3ClSi$: C, 49.51; H, 8.69; Cl, 13.29; Si, 10.53. Found: C, 49.61; H, 8.71; Cl, 13.67; Si, 10.01.

***tert*-Butyl *N*-((3*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}butoxycarbonyl)-3-({[(5*R*)-3-(4-cyanophenyl)-4,5-dihydro-5-isoxazolyl]acetyl}amino)-L-alaninate (27).** To a solution of **11** (0.90 g, 2.4 mmol) in 15 mL of THF was added a solution of **26** (0.65 g, 2.4 mmol) in 5 mL of THF, followed by a solution of Et_3N (0.25 g, 2.4 mmol) in 2 mL of THF at rt. After being stirred at rt for 1.5 h, the reaction mixture was treated with 60 mL of EtOAc and 30 mL of water. The layers were separated and the organic layer was washed with 10% citric acid (25 mL), water (25 mL), dried ($MgSO_4$) and evaporated to give 1.44 g of a yellow, foamy solid. Chromatography (silica gel, 10-50% EtOAc/hexane) gave **27** (1.07 g, 74% yield). **27:** mp 50-63 ^oC; ^1H NMR ($CDCl_3$) δ 7.71 (dd, J = 6.8, 2.0 Hz, 2H), 7.65 (dd, J = 6.8, 2.1 Hz, 2H), 6.32 (br, 1H), 5.54 (br d, J = 6.6 Hz, 1H), 5.15-5.05 (m, 1H), 4.28 (m, 1H), 4.08 (t, J = 6.4 Hz, 2H), 3.83 (m, 1H).; ^{13}C NMR ($CDCl_3$) δ 169.41, 156.73, 155.76, 133.65, 132.50, 127.20, 118.25, 113.60, 83.26, 78.59, 77.22, 65.31, 62.80, 42.28, 41.53, 39.45, 38.58, 27.94, 25.82, 24.02, 18.03, -4.38, -4.91; MS (AP^+) *m/z* 603.1 (M + H, 100); $[\alpha]_D^{25}$ -61.6^o (*c* 0.33, $CHCl_3$); IR (KBr) 3350, 2957, 2931, 2857, 2229, 1722, 1662, 1528, 1369, 1256, 1156, 1067, 838, 776 cm^{-1}. Anal. Calcd for $C_{30}H_{46}N_4O_7Si$: C, 59.78; H, 7.69; N, 9.30; Si, 4.66. Found: C, 59.72; H, 7.72; N, 9.30; Si, 4.58.

***tert*-Butyl 3-{[((5*R*)-3-{4-[(*E*)-amino(hydroxyimino)methyl]phenyl}-4,5-dihydro-5-isoxazolyl)acetyl]amino}-*N*-((3*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}butoxycarbonyl)-L-alaninate (28).** To a solution of **27** (1.01 g, 1.7 mmol) in 20 mL of MeOH was added hydroxylamine hydrochloride (0.47 g, 6.7 mmol) and Et_3N (0.68 g, 6.7 mmol) at rt. After 1 h of heating at reflux, the reaction mixture was cooled to rt, and the solvent in the mixture was evaporated. The residue was treated with EtOAc (25 mL) and water (25 mL). The layers were separated and the aqueous layer was extracted with EtOAc (1 x 25 mL). The combined organic layers were washed with water (25 mL), brine (25 mL), dried ($MgSO_4$) and evaporated to give **28** as a white foamy solid (1.01 g, 93% yield). **28:** mp 72-78 ^oC; ^1H NMR ($CDCl_3$) δ 7.57 (br, 1H), 7.57 (d, J = 6.9 Hz, 1H), 5.02 (m, 1H), 4.93 (m, 1H), 4.33 (m, 1H), 4.07 (t, J = 7.4 Hz, 2H), 3.87 (m, 1H), 3.69-3.54 (m, 2H), 3.38 (dd, J = 16.8, 10.2 Hz, 1H), 2.98 (dd, J = 16.8, 7.7 Hz, 1H), 2.61 (dd, J = 14.7, 6.6 Hz, 1H), 2.42, (dd, J = 14.9, 6.2 Hz, 1H), 1.64 (m, 2H), 1.43 (s, 9H), 1.10 (d, J = 6.3 Hz, 3H), 0.83 (s, 9H), 0.0 (s, 3H), -0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.42, 169.40, 156.40, 156.19, 152.05, 134.03, 130.70, 126.93, 126.10, 83.21, 77.98, 65.31, 62.79, 54.46, 41.95, 41.57, 39.92, 38.58, 27.94, 25.84, 24.03, 18.04, -4.39, -4.90; MS (AP^+) *m/z* 636.2 (M + H, 100); $[\alpha]_D^{25}$ -53.9^o (*c* 0.316, MeOH); IR (KBr) 3353, 2958, 2930, 1722, 1640, 1529, 1369, 1254, 1155, 1068, 838, 775 cm^{-1}. Anal. Calcd for $C_{30}H_{49}N_5O_8Si$: C, 56.67; H, 7.77; N, 11.02; Si, 4.42. Found: C, 56.57;

H, 7.86; N, 10.90; Si, 4.30.

***tert*-Butyl 3-{[((5*R*)-3-{4-[(*Z*)-[(acetyloxy)imino](amino)methyl]phenyl}-4,5-dihydro-5-isoxazolyl)acetyl]amino}-*N*-((3*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}butoxycarbonyl)-L-alaninate (29).** To an ice-cold solution of **28** (0.80 g, 1.26 mmol) in 10 mL of CH_2Cl_2 were added a solution of pyridine (0.15 g, 1.9 mmol) in 1 mL of CH_2Cl_2 and a solution of acetic anhydride (0.17 g, 1.6 mmol) in 1 mL of CH_2Cl_2. After the addition was completed, the mixture was further stirred for 1.5 h with an ice bath cooling. The reaction solution was treated with CH_2Cl_2 (30 mL) and water (20 mL). After the separation of the layers, the organic layer was washed with water (25 mL), brine (25 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (silica gel, 0-2% MeOH/ CH_2Cl_2) to give **29** (0.61 g, 72% yield) as a white foamy solid. **29:** mp 79 ^oC; ^1H NMR ($CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H), 6.38 (br, 1H), 5.57 (J = 7.0 Hz, 1H), 5.12 (br s, 2H), 5.09-5.01 (m, 1H), 4.28 (br, 1H), 4.09 (t, J = 6.6 Hz, 2H), 3.89 (q, J = 5.8 Hz, 1H), 3.60 (br, 2H), 3.49 (dd, J = 17.1, 10.5 Hz, 1H), 3.16 (dd, J = 17.1, 7.6 Hz, 1H), 2.65 (dd, J = 14.7, 6.6 Hz, 1H), 2.50 (dd, J = 14.8, 6.0 Hz, 1H), 2.22 (s, 3H), 1.69-1.64 (m 2H), 1.44 (s, 9H), 1.11 (d, J = 6.3 Hz, 3H), 0.84 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.72, 169.16, 168.73, 156.65, 156.30, 155.18, 132.62, 131.78, 127.04, 126.97, 83.14, 78.08, 77.20, 65.33, 62.75, 54.60, 42.04, 41.70, 39.89, 38.59, 27.95, 25.84, 24.03, 19.90, 18.04, -4.38, -4.89; MS (AP^+) *m/z* 678 (M + H, 30); $[\alpha]_D^{25}$ -81.3^o (*c* 0.314, MeOH); IR (KBr) 3341, 1724, 1640, 1535, 1368, 1252, 1156, 1069, 838, 775 cm^{-1}. Anal. Calcd for $C_{32}H_{51}N_5O_9Si$: C, 56.70; H, 7.58; N, 10.33; Si, 4.14. Found: C, 56.40; H, 7.58; N, 10.23; Si, 4.05.

***tert*-Butyl 3-{[((5*R*)-3-{4-[amino(imino)methyl]phenyl}-4,5-dihydro-5-isoxazolyl)acetyl]-amino}-*N*-((3*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}butoxycarbonyl)-L-alaninate (30).** To a solution of **29** (0.25 g, 0.37 mmol) in 12 mL of MeOH was added 5% palladium on carbon (50 mg). The mixture was hydrogenated at 20 psi at rt for 1 h. The catalyst was then removed by filtration. The solvent in the filtrate was evaporated to dryness to give **30** (0.23 g, 100% yield) as a white solid. **30:** mp 173-177 ^oC; ^1H NMR (CD_3OD) δ 7.85 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H), 5.10-5.02 (m, 1H), 4.17 (m, 1H), 4.02 (m, 1H), 3.93 (m, 1H), 3.60-3.47 (m, 2H), 3.36 (dd, J = 13.6, 8.1 Hz, 1H), 3.24-3.16 (m, 1H), 2.62 (dd, J = 14.5, 7.2 Hz, 1H), 2.48 (dd, J = 14.3, 6.2 Hz, 1H), 1.68-1.56 (m, 2H), 1.41 (s, 9H), 1.08 (d, J = 5.9 Hz, 3H), 0.82 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H); MS (AP^+) *m/z* 620.1 (M + H, 100), HRMS (ESI) *m/z* calcd for $C_{30}H_{50}N_5O_7Si$ [(M + H)] 620.3479, found 620.3485; $[\alpha]_D^{25}$ -75.7^o (*c* 0.334, MeOH); IR (KBr) 3304, 2958, 2930, 1699, 1652, 1554, 1414, 1369, 1255, 1157, 849, 837, 776 cm^{-1}.

3-{[((5*R*)-3-{4-[Amino(imino)methyl]phenyl}-4,5-dihydro-5-isoxazolyl)acetyl]amino}-*N*-{(3*R*)-3-[(trifluoroacetyl)oxy]butoxycarbonyl}-L-alanine trifluoroacetate (31). To an ice-cold

solution of **30** (0.1 g, 0.16 mmol) in 4 mL of CH_2Cl_2 was added 2 mL of TFA. The solution was stirred at 0 ^oC for 20 h and at rt for 24 h. The solvents in the reaction were evaporated to dryness. The residue was triturated with diethyl ether. The resulting white solid was collected on a filter to give **31** (93 mg, 88% yield) as a white solid. **31:** mp 151-156 ^oC; ^1H NMR (CD_3OD) δ 7.88 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.5 Hz, 2H), 5.17 (q, 1H, J = 6.3 Hz, 1H), 5.12-5.06 (m, 1H), 4.27 (m, 1H), 4.08 (t, J = 5.2 Hz, 2H), 3.71 (dd, J = 13.9, 4.4 Hz, 1H), 3.54 (dd, J = 17.2, 11.6 Hz, 1H), 3.37 (dd, J = 13.8, 7.9 Hz, 1H), 3.26-3.19 (m, 1H), 2.65 (dd, J = 14.5, 6.8 Hz, 1H), 2.50 (dd, J = 14.5, 6.8 Hz, 1H), 1.97 (m, 2H), 1.33 (d, J = 5.8 Hz, 3H); ^{13}C NMR (CD_3OD) δ 173.57, 172.67, 168.00, 158.79, 157.55, 136.45, 130.65, 129.48, 128.49, 80.22, 73.81, 65.44, 63.51, 55.36, 42.01, 41.76, 40.16, 39.29, 23.68; ^{19}F NMR (CD_3OD) δ -77.38, -77.49; MS (ES^+) *m/z* 546.2 (M + H, 100); HRMS (ESI) *m/z* calcd for $C_{22}H_{27}N_5O_8F_3$ [(M + H)] 546.1811, found 546.1817; $[\alpha]_D^{25}$ -70.5^o (*c* 0.304, MeOH); IR (KBr) 3317, 3105, 1782, 1667, 1541, 1205, 1189, 1136 cm^{-1}. Anal. Calcd for $C_{24}H_{27}N_5O_{10}F_6$: C, 43.71; H, 4.13; F, 17.26; N, 10.62. Found: C, 44.03; H, 4.14; F, 17.12; N, 10.67.

3-{[((5*R*)-3-{4-[Amino(imino)methyl]phenyl}-4,5-dihydro-5-isoxazolyl)-acetyl]amino}-*N*-((3*R*)-3-hydroxybutoxycarbonyl)-L-alanine trifluoroacetate (6b). A solution of **30** (0.1 g, 0.16 mmol) in 4 mL of CH_2Cl_2 and 2 mL of TFA was stirred at rt for 5 h. After evaporation of the solvent and excess TFA, the remaining white residue was added 10 mL of water and the resulting solution was stirred at rt for 3 h. The water in the solution was removed by lyophilization to give **6b** (85.3 mg, 95% yield) as a white solid. **6b:** mp 158-160 ^oC; ^1H NMR (DMSO-d_6) δ 9.41 (s, 2H), 9.26 (s, 2H), 8.16 (t, J = 5.7 Hz, 1H), 7.93 (d, J = 9.6 Hz, 2H), 7.91 (d, J = 9.5 Hz, 2H), 7.31 (d, J = 8.4 Hz, 1H), 5.08 (m, 1H), 4.14-4.12 (m, 1H), 4.05 (t, J = 6.8 Hz, 2H), 3.74 (q, J = 6.2 Hz, 1H), 3.62-3.57 (m, 2H), 3.32-3.23 (m, 2H), 2.64 (dd, J = 14.5, 6.4 Hz, 1H), 2.49 (dd, J = 14.5, 7.2 Hz, 1H), 1.65-1.59 (m, 2H), 1.11 (d, J = 6.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 171.98, 169.23, 164.98, 156.19, 156.05, 134.28, 129.06, 128.60, 126.77, 78.61, 62.83, 61.67, 53.64, 40.53, 39.63, 38.72, 38.13, 23.74; ^{19}F NMR (DMSO-d_6) δ -73.39; MS (ES^+) *m/z* 450.1 (M + H, 100); $[\alpha]_D^{25}$ -79.9^o (*c* 0.310, H_2O); IR (KBr) 3318, 3106, 1668, 1542, 1205, 1189, 1136, 849 cm^{-1}. Anal. Calcd for $C_{22}H_{28}N_5O_9F_3$: C, 46.89; H, 5.01; N, 12.43; F, 10.12. Found: C, 47.01; H, 5.01; N, 12.10; F, 9.96.

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