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Radical Functionalization of Unsaturated Amino Acids: Synthesis of Side-Chain-Fluorinated, Azido-Substituted, and Hydroxylated Amino Acids

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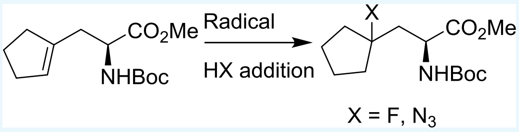
Supporting Information

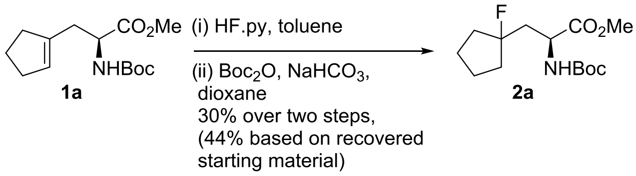


ABSTRACT: A range of enantiomerically pure protected side-chain-fluorinated amino acids has been prepared (13 examples) by treatment of protected amino acids containing unsaturated side chains with a combination of Fe(III)/NaBH$_4$ and Selectfluor. The modification of the conditions by replacement of Selectfluor with NaN$_3$ allowed the preparation of side-chain azido-substituted amino acids (five examples), which upon catalytic hydrogenation gave the corresponding amines, isolated as lactams (four examples). Radical hydration of the unsaturated side chains leading to side-chain-hydroxylated protected amino acids has also been demonstrated.

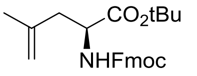
INTRODUCTION

The synthesis of enantiomerically pure amino acids continues to attract substantial attention, and the development of new methods for the preparation of side-chain-functionalized amino acids is the focus of much effort.[1] In particular, the synthesis of amino acids with side-chain fluorine substitution has been widely studied,[2] specifically in the context of the preparation of (*S*)-*γ*-fluoroleucine, a component of the Merck Cathepsin K inhibitor odanacatib.[3] An early approach to (*S*)-*γ*-fluoroleucine ethyl ester relied on the use of the Schöllkopf bis-lactim ether.[4] The synthetic routes that have been developed more recently include the use of aspartic acid as a chiral pool starting material,[5] a titanium-catalyzed asymmetric ene-reaction,[6] use of glycine-Schiff base alkylation followed by enzymatic resolution,[7] and more recently direct photochemical fluorination of leucine itself.[8] This followed an earlier indirect method which employed photochemical bromination of leucine, followed by treatment with AgF.[9] The latter two approaches rely on the selective radical cleavage of the tertiary C−H bond of leucine for their success. A complementary method makes use of AgF/tetra-*n*-butylammonium fluoride as the fluorine source, in conjunction with a manganese porphyrin catalyst.[10] In previous work, we have reported a single example of the synthesis of the *γ*-fluorinated cyclopentylalanine derivative **2a** using the ionic addition of hydrogen fluoride (HF) (using HF-pyridine) to an unsaturated amino acid **1a** (Scheme 1).[11] This compound was a key component of a Cathepsin S inhibitor. Although this synthetic approach was rather inefficient, largely due to the in situ *tert*-butoxycarbonyl (Boc)-deprotection of the substrate under the conditions of the reaction, it was nevertheless a very considerable improvement over the previous method used for making this protected amino acid.[12]

Scheme 1. Original Ionic Method for the Preparation of *tert*-Fluoride 2a



The report by Barker and Boger on the new radical addition of HF to unactivated alkenes, using Fe(III)/NaBH$_4$, with Selectfluor as the fluorine source,[13] prompted us to revisit our general strategy. Indeed, after we had completed the majority of the work reported in this paper, another group reported the application of the Barker and Boger method to the synthesis of Fmoc-(*S*)-*γ*-fluoroleucine **4** (in presumed 94% enantiomeric excess (ee), based on the ee of the starting material), using the 2-propenylalanine derivative **3**.[14] We now report an in-depth study of this reaction, to assess its generality and scope for the preparation of side-chain-fluorinated amino acids as well as a possible extension by trapping the intermediate alkyl radicals to allow the introduction of other functional groups into the amino acid side chains, by exploring the use of subsequently reported variants of the Boger process.[15]



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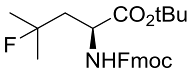

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RESULTS AND DISCUSSION

Preparation of Unsaturated Amino Acids. The initial goal was to prepare a representative selection of protected enantiomerically pure unsaturated amino acids, with double bonds at both the γ- and δ-positions. A range of cycloalkenylalanine derivatives was prepared by room-temperature Negishi cross-coupling of cycloalkenyl triflates (**5a**−**d**, **6**, and **7**) with the serine-derived zinc reagent **8**, according to our previously reported methods from the protected iodoalanine derivative **9** (Scheme 2, Table 1).[16] It was established that extending the reaction times for the cross-coupling generally resulted in higher isolated yields of the desired products (**1a**−**d**) than we had previously observed.[11,16] In addition, two more functionalized vinyl triflates **6** and **7** were successfully coupled, giving the corresponding protected amino acids **10** and **11**.

Scheme 2. Negishi Cross-Coupling with Cycloalkenyl Triflates

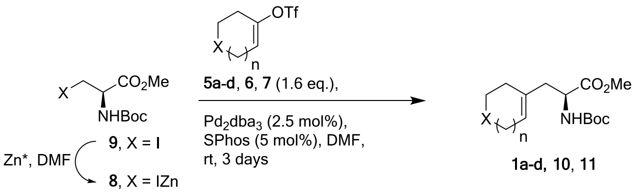


Table 1. Negishi Coupling of Zinc Reagent 8 with Cycloalkenyl Triflates

entry	substrate	X	*n*	product	yield (%)
1	**5a**	CH_2	0	**1a**	83 (70)[a]
2	**5b**	CH_2	1	**1b**	92 (70)[a]
3	**5c**	CH_2	2	**1c**	81 (62)[a]
4	**5d**	CH_2	3	**1d**	61 (63)[a]
5	**6**	O	1	**10**	52
6	**7**	CF_2	1	**11**	90

[a] Yield obtained under previous conditions.[11]

Although there is less precedent for the use of vinyl bromides in the Negishi cross-coupling with zinc reagent **8**, a range of vinyl bromides (**12**−**15**) was successfully coupled under the same conditions that we had employed for coupling the vinyl triflates to give the expected unsaturated amino acids (**16**−**19**) (Scheme 3, Table 2). The cross-coupling reactions of (*E*)- and (*Z*)-2-bromo-2-butene with zinc reagent **8** were stereospecific, leading to the isomeric products (***E***)**-18** and (***Z***)**-18**, respectively. Interestingly, the use of an excess of the commercially available isomeric mixture of 2-bromo-2-butene (E/Z, 1.9:1, as determined by ^{1}H NMR, with both isomers used in excess relative to zinc reagent **8**) in the cross-coupling resulted in the formation of a mixture of the products **18** that was substantially enriched in the (E)-isomer (E/Z, 7:1) (Table 2, entry 5), indicating that the Negishi cross-coupling of the zinc reagent **8** with (*E*)-2-bromo-2-butene (***E***)**-14** was faster than with (Z)-isomer 2-bromo-2-butene (***Z***)**-14** (by a factor of 3.5). This most likely reflects a faster rate of oxidative addition of the less hindered (E)-isomer of compound **14** to Pd. The most notable example was the successful cross-coupling of zinc reagent **8** with 1-bromocyclobutene **15** leading to the cyclobutenyl alanine derivative **19**, which is a rare example of the use of 1-bromocyclobutene in the Negishi cross-coupling.

Scheme 3. Negishi Cross-Coupling with Vinyl Bromides

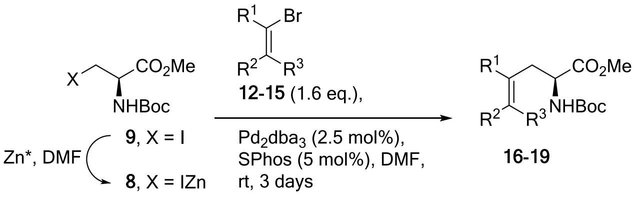
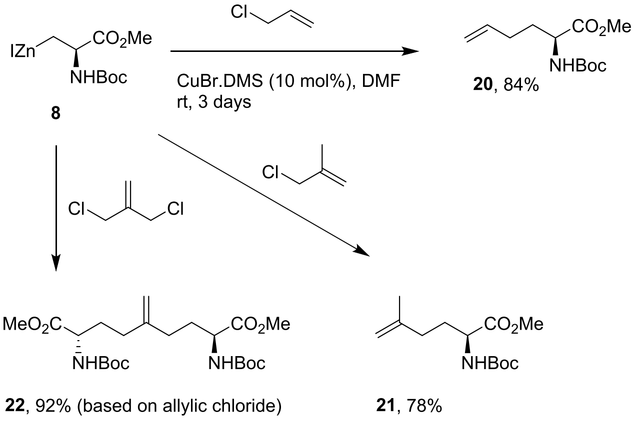


Table 2. Negishi Coupling of Zinc Reagent 8 with Vinyl Bromides

entry	substrate	R^1	R^2	R^3	product	yield (%)
1	**12**	Me	H	H	**16**	84
2	**13**	H	Me	Me	**17**	95
3	(*E*)-**14**	Me	Me	H	(*E*)-**18**	68
4	(*Z*)-**14**	Me	H	Me	(*Z*)-**18**	72
5	(*E*,*Z*)-**14**	Me	Me/H		(*E*,*Z*)-**18**	88
6	**15**	$(CH_2)_2$		H	**19**	79

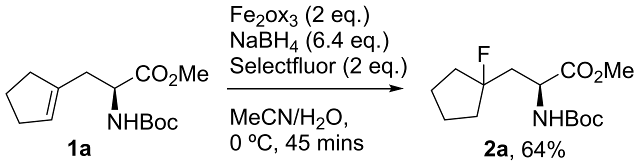
A small selection of unsaturated amino acid substrates **20**−**22** was prepared by our previously reported method using copper-catalyzed allylation of the zinc reagent **8** (Scheme 4).[17] Again, we observed that extended reaction times at room temperature resulted, in most cases, in improved yields over those we had previously observed.

Scheme 4. Cu(I)-Catalyzed Allylation of Zinc Reagent 8



Radical Addition of HF to Unsaturated Amino Acids. Barker and Boger's original report contained examples of the radical HF-addition to terminal alkenes containing an ester or a protected amine as well as a dipeptide in which the terminal alkene was incorporated into a tyrosine residue.[13] Therefore, it was reasonable that unsaturated amino acid substrates would also undergo the reaction. In the event, the application of the conditions reported by Barker and Boger to the cyclopentenylalanine derivative **1a** resulted in the formation of **2a**, identical to the material we had previously prepared,[11] but in substantially higher yield (64%) and without unproductive protecting group removal and using less toxic reagents (Scheme 5). The structure of compound **2a** was confirmed by X-ray analysis and showed a hydrogen bond from the carbamate N−H to the carbamate carbonyl of the neighboring molecule as well as a very distinct alignment of the C−F bond with the C−F bond of the closest neighbor.

Scheme 5. Radical Hydrofluorination of Cyclopentenylalanine 1a

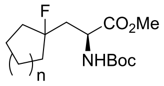


We were pleased to find that with the exception of the 4,4-difluorocyclohexen-1-yl alanine derivative **11** (vide infra), the procedure proved applicable to the other substrates that we had prepared, giving the desired HF-addition products in good to excellent yields (Table 3). To establish whether or not the reaction proceeded without racemization, both enantiomers of the 3-methyl-3-butenylglycine derivatives **16** and ***ent*-16** were each separately subjected to the radical HF-addition conditions; the products **25** and ***ent*-25** were obtained with high ee (99 and 98%, respectively, as determined by chiral phase high-performance liquid chromatography (HPLC)), thus establishing that the reaction did indeed proceed without racemization. When the two isomeric alkene substrates **17** and **21** were separately subjected to the radical HF-addition conditions, the same *tert*-fluoride **26** was obtained, with a slightly higher yield from the starting material **17** with the more substituted double bond (cf. entries 9 and 13, Table 3). When the radical HF-addition was attempted on the 4,4-difluorocyclohexen-1-yl alanine derivative **11**, the conversion was incomplete and purification difficult. We, therefore, modified the procedure by increasing the amounts of Fe(III) and Selectfluor and by the dropwise addition of a solution of $NaBH_4$ (in 0.1 M NaOH) over a period of 6 h, which resulted in the isolation of the desired product **24** in comparable yield to that obtained with the other substrates. This modified procedure may be successful with other more challenging substrates. The X-ray crystal structure of compound **24** was obtained, confirming the structure and showing similar intermolecular interactions in the solid state to those observed in the X-ray structure of **2a**.

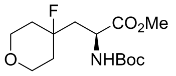
Table 3. Radical Hydrofluorination of Unsaturated Substrates

entry	substrate	product	yield (%)
1	**1a**	**2a**	64
2	**1b**	**2b**	64
3	**1c**	**2c**	70
4	**1d**	**2d**	65
5	**10**	**23**	54
6	**11**	**24**	0 (64)[a]
7	**16**	**25**	84
8	***ent*-16**	***ent*-25**	88
9	**17**	**26**	75
10	**18**	**27**	63
11	**19**	**28**	81
12	**20**	**29**	73
13	**21**	**26**	62
14	**22**	**30**	91

[a] Reaction carried out by increasing the molar equivalents of Fe(III) and Selectfluor and by the dropwise addition of a solution of $NaBH_4$ (in 0.1 M NaOH).



2a, n = 1
2b, n = 2
2c, n = 3
2d, n = 4



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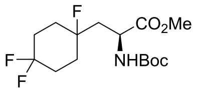

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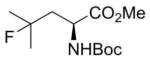

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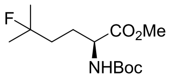

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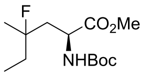

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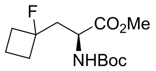

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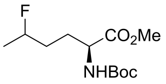

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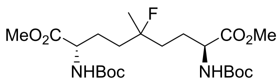

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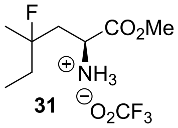
The addition of HF to the substrates **18** and **20** resulted in the formation of products **27** and **29** each with a new stereogenic center. In each case, the removal of the Boc-protecting group with trifluoroacetic acid (TFA) to give the corresponding trifluoroacetate salts, **31** and **32,** followed by analysis by NMR methods established that, in each case, the new stereogenic center had been formed with very low diastereomeric excess (de) (specifically less than 5% de), entirely consistent with the results of Barker and Boger.[13]



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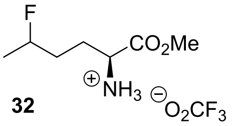

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Radical Addition of HN_3 to Unsaturated Amino Acids.

Given the efficiency of the radical addition of HF to unsaturated amino acids and the precedent from Leggans et al. that a combination of Fe(III)/$NaBH_4$ and NaN_3 as the azide source promoted the efficient radical addition of HN_3 to alkenes,[15] we have explored the application of this method to the functionalization of unsaturated amino acids. The formation of amino acids with side-chain nitrogen functionality is of interest, since the compounds are analogues of lysine. Direct application of the literature protocol for the hydroazidation of citronellol[15] to unsaturated amino acid **16** resulted in the incomplete conversion of the starting materials. However, a minor modification, in which the excess of reagents was increased, resulted in a very efficient conversion of **16** to the corresponding tertiary azide **33**. The application of this modified method to a representative selection of unsaturated amino acids resulted, in each case, in the formation of the expected tertiary azide in good to excellent yields (Scheme 6, Table 4). The two isomeric alkenes **17** and **21** gave the same tertiary azide **36**, with a slightly higher yield being observed when using the more substituted alkene **17** (Scheme 7), as already observed during the HF-addition to the same substrates.

Scheme 6. Radical Hydroazidation of Unsaturated Substrates

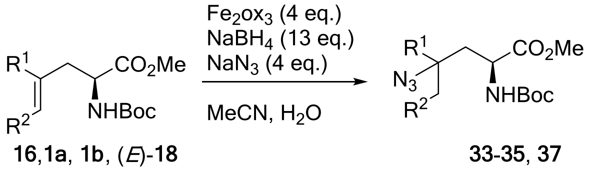
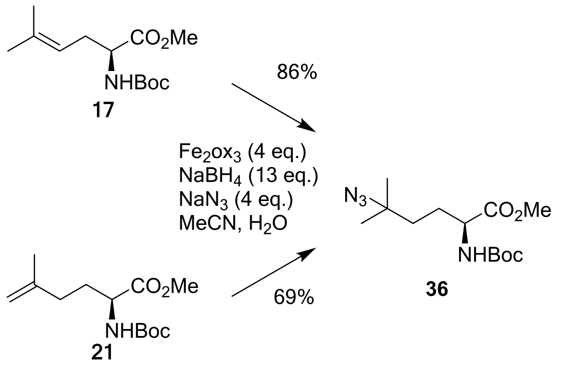


Table 4. Radical Hydroazidation of Unsaturated Substrates

entry	substrate	R^1	R^2	product	yield (%)
1	**16**	Me	H	**33**	88
2	**1a**	$(CH_2)_3$		**34**	88
3	**1b**	$(CH_2)_4$		**35**	71
4	(*E*)-**18**	Me	Me	**37**	63

Scheme 7. Alternative Approaches to Tertiary Azide 36



Each of the azides **33**−**36** was reduced by catalytic hydrogenation to give the corresponding free amines, which underwent spontaneous cyclization to give the corresponding lactams **38**−**41**, which were each isolated in high yields (Scheme 8, Table 5). The structure of the lactam **40** was confirmed by single-crystal X-ray structure analysis.

Scheme 8. Hydrogenation of Azido Amino Acids

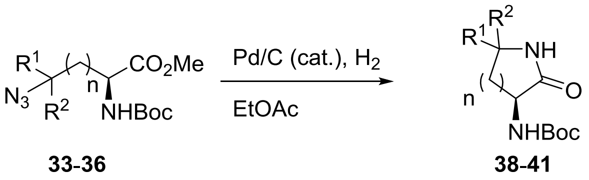
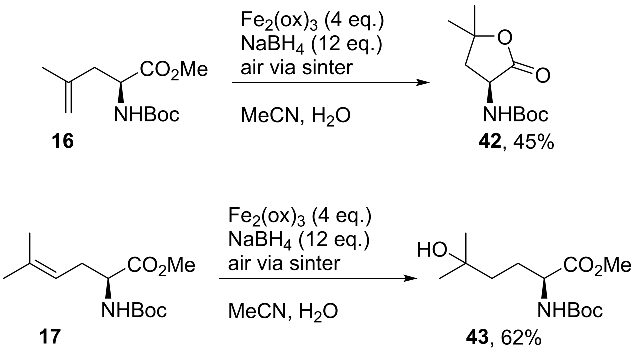


Table 5. Hydrogenation of Azides

entry	substrate	R^1	R^2	*n*	product	yield (%)
1	**33**	Me	Me	1	**38**	99
2	**34**	$(CH_2)_4$		1	**39**	93
3	**35**	$(CH_2)_5$		1	**40**	91
4	**36**	Me	Me	2	**41**	98

Radical Alkene Hydration. The final transformation that we briefly investigated was the radical hydration of unsaturated amino acids using the combination of Fe(III)/$NaBH_4$ and air as a radical trap.[15] Such a process would lead to amino acids with a side-chain hydroxyl group. The optimization of this particular radical addition process proved challenging and appeared to be critically dependent on the means by which the air was introduced into the reaction mixture. Most reliable results were obtained when the air was introduced using a sintered gas inlet, and in two cases (using **16** and **17** as substrates), moderate yields of the corresponding hydroxylated amino acids were obtained, albeit isolated as the corresponding lactone **42** in one case (Scheme 9).

Scheme 9. Radical Hydration of Unsaturated Amino Acids



CONCLUSIONS

In conclusion, the generality and scope of the radical HF-addition to unsaturated amino acid substrates have been established, further demonstrating the functional group tolerance of the Boger radical hydrofluorination process. In combination with our previously reported methods for the preparation of unsaturated amino acids (extended to the Negishi cross-coupling with vinyl bromides in this paper), this constitutes an effective and direct method for the preparation of important side-chain-fluorinated amino acid derivatives. Furthermore, radical hydroazidation of unsaturated amino acid substrates has been demonstrated, allowing the synthesis of side-chain amino-substituted amino acids. Finally, radical hydration of unsaturated amino acid substrates has been demonstrated, but further work is required to establish the full scope of this transformation.

EXPERIMENTAL SECTION

High-resolution mass spectrometry (HRMS) measurements were carried out using electrospray (ES) ionization, with a time-of-flight mass analyzer. IR spectra were recorded as thin films or using attenuated total reflection. The synthesis of *N*-Boc-*β*-I-Ala-OMe was accomplished by the literature methods.[18] For the preparation of zinc reagent **8** and general procedures A, B, and F, flame-dried glassware was used. Cycloalkenyl triflates **5a**−**d** were prepared by general literature methods[19] from the corresponding ketones and used without purification. Triflates **6**,[20] **7**[21] and 1-cyclobutenyl bromide **15**[22] were each prepared by literature methods.

Preparation of Zinc Reagent 8. Zinc powder (3 equiv) was suspended in dry dimethylformamide (DMF) (3 mL) under nitrogen, and iodine (nine crystals) was added immediately. A change in color from colorless to dark brown and colorless again was observed. *N*-Boc-*β*-I-Ala-OMe **9** (1 equiv) was added followed immediately by iodine (three crystals), the aforementioned color change was observed once more, and the insertion process was allowed to proceed for 30−60 min.

General Procedure A, Coupling of 8 to Vinyl Triflates and Halides. Immediately after the preparation of **8**, $Pd_2(dba)_3$ (2.5 mol %) and SPhos (5.0 mol %) were added to the reaction vessel along with an excess vinyl halide/triflate (≈1.6 equiv), as indicated in the individual procedures below. The reaction mixture was stirred under a gentle flow of nitrogen for 72 h. The reaction mixture was then filtered through a silica plug eluting with EtOAc. The organic phase was washed with water (2 × 50 mL) and brine (50 mL). The organic phase was dried with Na_2SO_4, filtered, and the solvent removed under reduced pressure. Purification was carried out by flash column chromatography (EtOAc in petroleum ether (40−60) mixtures over silica).

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Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(cyclopent-1-en-1-yl)propanoate 1a. Synthesis was achieved by general procedure A using zinc dust (0.217 g, 3.32 mmol), iodine (2 crystals, then 1 crystal), **9** (0.325 g, 0.99 mmol), $Pd_2(dba)_3$ (0.024 g, 0.03 mmol), SPhos (0.023 g, 0.06 mmol), and **5a** (0.375 g, 1.73 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **1a** as a light orange oil (0.220 g, 0.82 mmol, 83%); $[\alpha]_D^{25}$ +17.0 (*c* 2.00, $CHCl_3$), [lit. $[\alpha]_D^{22}$ +13.9 (*c* 2.09, $CHCl_3$)];[16] ν_{max}(ATR)/cm^{-1} 3371, 2974, 2951, 2932, 2848, 1744, 1713, 1501, 1436, 1392, 1365, 1248, 1211, 1160, 1056, 1020, 860, 778, and 759; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.47 (s, 1H), 4.98 (d, *J* = 7.8 Hz, 1H), 4.41 (m, 1H), 3.73 (s, 3H), 2.59 (dd, *J* = 14.2 Hz, 4.8 Hz, 1H), 2.49 (dd, *J* = 14.4 Hz, 7.5 Hz, 1H), 2.33−2.16 (m, 4H), 1.86 (apparent quin, *J* = 7.4 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.2, 155.2, 139.0, 128.3, 79.8, 52.2, 52.1, 34.7, 34.2, 32.5, 28.3, 23.6; HRMS (ES) *m*/*z*: $[M + Na]^+$ calcd for $C_{14}H_{23}NO_4Na$ 292.1519; found 292.1523.

The characterization data was consistent with that reported in the literature.[16]

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(cyclohex-1-en-1-yl)propanoate 1b. Synthesis was achieved by general procedure A using zinc dust (0.606 g, 9.27 mmol), iodine (6 crystals, then 4 crystals), **9** (1.013 g, 3.08 mmol), $Pd_2(dba)_3$ (0.068 g, 0.07 mmol), SPhos (0.069 g, 0.17 mmol), and **5b** (1.283 g, 5.57 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **1b** as a light orange oil (0.798 g, 2.82 mmol, 92%); $[\alpha]_D^{24}$ +14.1 (*c* 0.99, $CHCl_3$), [lit. $[\alpha]_D^{22}$ +14.5 (*c* 1.68, $CHCl_3$)];[16] ν_{max}(ATR)/cm^{-1} 3355, 2976, 2929, 2859, 2838, 1744, 1713, 1504, 1437, 1391, 1365, 1275, 1258, 1215, 1161, 1084, 1048, 1020, 920 and 863; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.48 (s, 1H), 4.92 (d, *J* = 7.6 Hz, 1H), 4.39 (m, 1H), 3.74 (s, 3H), 2.43 (dd, *J* = 13.5 Hz, 5.2 Hz, 1H), 2.26 (dd, *J* = 13.5 Hz, 8.6 Hz, 1H), 2.00−1.88 (m, 4H), 1.68−1.52 (m, 4H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.4, 155.2, 132.7, 125.7, 79.8, 52.1, 51.9, 41.4, 28.3, 27.8, 25.3, 22.7, 22.1; HRMS (ES) *m*/*z*: $[M + Na]^+$ calcd for $C_{15}H_{25}NO_4Na$ 306.1681; found 306.1676.

The characterization data was consistent with that reported in the literature.[16]

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(cyclohept-1-en-1-yl)propanoate 1c. Synthesis was achieved by general procedure A using zinc dust (0.791 g, 12.10 mmol), iodine (12 crystals, then 5 crystals), **9** (1.330 g, 4.04 mmol), $Pd_2(dba)_3$ (0.094 g, 0.10 mmol), SPhos (0.112 g, 0.27 mmol), and **5c** (1.609 g, 6.59 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **1c** as a light orange oil (0.981 g, 3.30 mmol, 82%); $[\alpha]_D^{24}$ +8.4 (*c* 1.08, $CHCl_3$), [lit. $[\alpha]_D^{22}$ +7.8 (*c* 1.15, $CHCl_3$)];[16] ν_{max}(ATR)/cm^{-1} 3367, 2975, 2919, 2846, 1744, 1712, 1498, 1438, 1389, 1365, 1248, 1212, 1159, 1050, 1022, 994 and 852; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.62 (t, *J* = 6.2 Hz, 1H), 4.93 (d, *J* = 7.1 Hz, 1H), 4.34 (m, 1H), 3.73 (s, 3H), 2.46 (dd, *J* = 13.2 Hz, 5.6 Hz, 1H), 2.27 (dd, *J* = 13.3 Hz, 8.3 Hz, 1H), 2.14−2.06 (m, 4H), 1.76−1.70 (m, 2H), 1.44−1.35 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.4, 155.2, 139.3, 131.0, 79.8, 52.1, 52.0, 43.4, 32.4, 32.3, 28.5, 28.3, 27.0, 26.5; HRMS (ES) *m*/*z*: $[M + Na]^+$ calcd for $C_{16}H_{27}NO_4Na$ 320.1838; found 320.1833.

The characterization data was consistent with that reported in the literature.[16]

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(cyclooct-1-en-1-yl)propanoate 1d. Synthesis was achieved by general procedure A using zinc dust (0.596 g, 9.11 mmol), iodine (9 crystals, then 5 crystals), **9** (0.990 g, 3.01 mmol), $Pd_2(dba)_3$ (0.074 g, 0.08 mmol), SPhos (0.066 g, 0.16 mmol), and **5d** (1.311 g, 5.08 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **1d** as a light orange oil (0.572 g, 1.84 mmol, 61%); $[\alpha]_D^{24}$ +7.8 (*c* 1.15, $CHCl_3$), [lit. $[\alpha]_D^{22}$ +9.5 (*c* 0.53, $CHCl_3$)];[16] ν_{max}(ATR)/cm^{-1} 3365, 2977, 2923, 2851, 1745, 1714, 1501, 1469, 1436, 1391, 1365, 1248, 1216, 1160, 1057, 1023, 894, and 861; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.42 (t, *J* = 8.0 Hz, 1H), 4.90 (d, *J* = 7.2 Hz, 1H), 4.35 (m, 1H), 3.73 (s, 3H), 2.50 (dd, *J* = 13.8 Hz, 4.9 Hz, 1H), 2.26 (dd, *J* = 13.7 Hz, 9.1 Hz, 1H), 2.15−2.08 (m, 4H), 1.54−1.47 (m, 8H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.4, 155.2, 135.6, 128.7, 79.8, 52.1, 52.0, 40.3, 29.7, 28.5, 28.3, 26.4, 26.3, 26.2; HRMS (ES) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{30}NO_4$ 312.2175; found 312.2183.

The characterization data was consistent with that reported in the literature,[16] with the exception of the ^{13}C NMR shifts. In the previous report, a signal at δ_C 22.8 was assigned to the compound, but this was not observed in our purified sample, and is, therefore, due to an impurity; heteronuclear single quantum coherence analysis established that the true signal was, in fact, obscured by the *tert*-butyl methyl signal.

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(3,6-dihydro-*2H*-pyran-4-yl)propanoate 10. Synthesis was achieved by general procedure A using zinc dust (1.484 g, 22.69 mmol), iodine (12 crystals, then 6 crystals), **9** (2.507 g, 7.62 mmol), $Pd_2(dba)_3$ (0.168 g, 0.18 mmol), SPhos (0.153 g, 0.37 mmol), and **6** (2.620 g, 11.28 mmol). Purification by flash column chromatography (25% EtOAc in petroleum ether (40−60), over silica) gave **10** as a colorless oil (1.132 g, 3.97 mmol, 52%); $[\alpha]_D^{25}$ +18.6 (*c* 1.02, $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3340, 3003, 2977, 2930, 2853, 1743, 1709, 1511, 1436, 1391, 1365, 1249, 1215, 1160, 1126, 1054, 1024, 1000, 849 and 752; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.52 (m, 1H), 5.00 (d, *J* = 7.7 Hz, 1H), 4.42 (m, 1H), 4.11 (m, 2H), 3.77 (m, 5H), 2.50 (dd, *J* = 13.9 Hz, 4.6 Hz, 1H), 2.32 (dd, *J* = 14 Hz, 8.5 Hz, 1H), 2.08 (m, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.1, 155.2, 130.9, 124.1, 80.0, 65.4, 64.3, 52.3, 51.7, 40.44, 28.3, 27.9; HRMS (ES) *m*/*z*: $[M + Na]^+$ calcd for $C_{14}H_{23}NO_5Na$ 308.1474; found 308.1485.

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(4,4-difluorocyclohex-1-en-1-yl)propanoate 11. Synthesis was achieved by general procedure A using zinc dust (0.615 g, 9.41 mmol), iodine (10 crystals, then 3 crystals), **9** (1.046 g, 3.18 mmol), $Pd_2(dba)_3$ (0.066 g, 0.07 mmol), SPhos (0.075 g, 0.18 mmol), and **7** (1.313 g, 4.93 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **11** as a colorless oil (0.914 g, 2.86 mmol, 90%); $[\alpha]_D^{24}$ +25.6 (*c* 1.02, $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3353, 2980, 1744, 1711, 1504, 1437, 1365, 1264, 1250, 1216, 1160, 1108, 1069, 1014, 971, 889, 860, and 777; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.36 (m, 1H), 4.97 (br d, *J* = 7.9 Hz, 1H), 4.46 (m, 1H), 3.75 (s, 3H), 2.51 (m, 3H), 2.38−2.25 (m, 3H), 2.09−1.98 (m, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 172.9, 155.1, 132.7, 122.7 (t, *J* = 240 Hz), 120.4, 80.0, 52.3, 51.8, 40.6, 34.7 (t, *J* = 27 Hz), 30.3 (t, *J* = 24 Hz), 28.3, 26.1 (t, *J* = 5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, 377 MHz) δ_F −95.7 (d, *J* = 235 Hz, 1 F), −97.3 (d, *J* = 235 Hz, 1 F); HRMS

(ES) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{24}F_2NO_4$ 320.1673; found 320.1679.

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-methylpent-4-enoate 16. Synthesis was achieved by general procedure A using zinc dust (1.966 g, 30.07 mmol), iodine (15 crystals, then 6 crystals), **9** (3.292 g, 10.00 mmol), $Pd_2(dba)_3$ (0.229 g, 0.25 mmol), SPhos (0.211 g, 0.51 mmol), and 2-bromopropene **12** (0.9 mL, 1.226 g, 10.13 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **16** as a light orange oil (2.051 g, 8.43 mmol, 84%); $[\alpha]_D^{24}$ +10.5 (*c* 1.05, $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3379, 2977, 2956, 2932, 1744, 1713, 1500, 1437, 1365, 1247, 1215, 1160, 1046, 1020, 895, 861, 779 and 759; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 4.96 (d, *J* = 6.6 Hz, 1H), 4.86 (s, 1H), 4.76 (s, 1H), 4.41 (m, 1H), 3.73 (s, 3H), 2.52 (dd, *J* = 13.8 Hz, 5.4 Hz, 1H), 2.37 (dd, *J* = 13.8 Hz, 8.3 Hz, 1H), 1.74 (s, 3H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.1, 155.3, 140.5, 114.5, 79.9, 52.2, 51.8, 40.7, 28.3, 21.8; HRMS (ES) *m*/*z*: $[M + Na]^+$ calcd for $C_{12}H_{21}NO_4Na$ 266.1363; found 266.1365.

Methyl (2*R*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-methylpent-4-enoate *ent*-16. Synthesis was achieved by general procedure A using zinc dust (0.607 g, 9.28 mmol), iodine (9 crystals, then 3 crystals), (*S*)-*N*-Boc-*β*-I-Ala-OMe ***ent*-9** (1.027 g, 3.12 mmol), $Pd_2(dba)_3$ (0.076 g, 0.08 mmol), SPhos (0.067 g, 0.16 mmol), and 2-bromopropene **12** (0.45 mL, 0.613 g, 5.07 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave ***ent*-16** as a light orange oil (0.729 g, 3.00 mmol, 96%); $[\alpha]_D^{24}$ −10.1 (*c* 1.48, $CHCl_3$).

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-5-methylhex-4-enoate 17. Synthesis was achieved by general procedure A using zinc dust (0.594 g, 9.08 mmol), iodine (6 crystals, then 3 crystals), **9** (1.006 g, 3.06 mmol), $Pd_2(dba)_3$ (0.070 g, 0.08 mmol), SPhos (0.065 g, 0.16 mmol), and 1-bromo-2-methyl-1-propene **13** (0.614 g, 4.55 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **17** as a light orange oil (0.748 g, 2.91 mmol, 95%); $[\alpha]_D^{24}$ +28.6 (*c* 1.05, $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3358, 2976, 2918, 1744, 1702, 1498, 1437, 1366, 1352, 1273, 1248, 1208, 1162, 1111, 1059, 1023, 860 and 754; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.02 (m, 2H), 4.34 (m, 1H), 3.72 (s, 3H), 2.53 (m, 1H), 2.41 (m, 1H), 1.70 (d, *J* = 0.8 Hz, 3H), 1.6 (s, 3H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 172.9, 155.3, 136.3, 117.6, 79.8, 53.3, 52.2, 30.9, 28.3, 25.9, 17.8; HRMS (ES) *m*/*z*: $[M + Na]^+$ calcd for $C_{13}H_{23}NO_4Na$ 280.1519; found 280.1524.

This reaction was also carried out on a larger scale using **9** (3.292 g, 10.00 mmol) and analogous equivalents of reagents, giving **17** (2.310 g, 8.98 mmol, 90%).

Methyl (2*S*,4*E*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-methylhex-4-enoate (*E*)-18. Synthesis was achieved by general procedure A using zinc dust (0.233 g, 3.56 mmol), iodine (4 crystals, then 2 crystals), **9** (0.339 g, 1.03 mmol), $Pd_2(dba)_3$ (0.026 g, 0.03 mmol), SPhos (0.023 g, 0.06 mmol), and (*E*)-2-bromo-2-butene **14** (0.12 mL, 0.159 g, 1.18 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **(*E*)-18** as a light orange oil (0.181 g, 0.70 mmol, 68%); $[\alpha]_D^{24}$ +10.0 (*c* 1.20, $CHCl_3$); ν_{max}(thin film, NaCl plates)/cm^{-1} 3443, 3372, 2978, 2930, 2862, 1747, 1718, 1503, 1438, 1366, 1250, 1218, 1170, 1060 and 1019; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.26 (q, *J* = 6.0 Hz, 1H), 4.91 (d, *J* = 7.4 Hz, 1H), 4.34 (m, 1H), 3.70 (s, 3H), 2.45 (dd, *J* = 13.4 Hz, 5.3 Hz, 1H), 2.27 (dd, *J* = 13.4 Hz, 8.5 Hz, 1H), 1.6 (m, 3H), 1.57 (d, *J* = 6.7 Hz, 3H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.3, 155.2, 130.7, 123.2, 79.7, 52.1, 52.0, 42.7, 28.3, 15.3, 13.5; HRMS (ES) *m*/*z*: $[M + Na]^+$ calcd for $C_{13}H_{23}NO_4Na$ 280.1519; found 280.1521.

Methyl (2*S*,4*E*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-methylhex-4-enoate (*Z*)-18. Synthesis was achieved by general procedure A using zinc dust (0.623 g, 9.53 mmol), iodine (10 crystals, then 3 crystals), **9** (1.000 g, 3.04 mmol), $Pd_2(dba)_3$ (0.072 g, 0.08 mmol), SPhos (0.068 g, 0.17 mmol), and (*Z*)-2-bromo-2-butene **14** (0.50 mL, 0.666 g, 4.93 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **(*Z*)-18** as a light orange oil (0.564 g, 2.19 mmol, 72%); $[\alpha]_D^{23}$ +13.7 (*c* 1.38, $CHCl_3$); ν_{max}(thin film, NaCl plates)/cm^{-1} 3445, 3373, 2977, 2930, 2865, 1747, 1717, 1505, 1453, 1438, 1367, 1278, 1251, 1208, 1169, 1086, 1052, 1021, 861 and 779; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.39 (q, *J* = 6.6 Hz, 1H), 4.97 (d, *J* = 7.7 Hz, 1H), 4.40 (m, 1H), 3.72 (s, 3H), 2.52 (dd, *J* = 13.6 Hz, 6.2 Hz, 1H), 2.42 (dd, *J* = 13.2 Hz, 7.8 Hz, 1H), 1.68 (m, 3H), 1.56 (d, *J* = 6.6 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.3, 155.2, 130.5, 123.5, 79.8, 52.2, 52.0, 34.3, 28.3, 23.3, 13.4; HRMS (ES) *m*/*z*: $[M + Na]^+$ calcd for $C_{13}H_{23}NO_4Na$ 280.1519; found 280.1520.

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(cyclobut-1-en-1-yl)propanoate 19. Synthesis was achieved by general procedure A using zinc dust (0.592 g, 9.06 mmol), iodine (9 crystals, then 6 crystals), **9** (0.988 g, 3.00 mmol), $Pd_2(dba)_3$ (0.070 g, 0.08 mmol), SPhos (0.063 g, 0.17 mmol), and 1-bromo-1-cyclobutene **15** (2.6 M in tetrahydrofuran, 0.38 mL, 0.99 mmol). Purification by flash column chromatography (8% EtOAc in petroleum ether (40−60), over silica) initially gave the product and *N*-Boc-Ala-OMe as a mixture. Further purification by flash column chromatography (CH_2Cl_2, over silica) gave **19** as a colorless oil (0.201 g, 0.79 mmol, 80%); $[\alpha]_D^{24}$ +20.2 (*c* 1.19, $CHCl_3$); ν_{max}(thin film, NaCl plates)/cm^{-1} 3362, 2978, 2953, 2929, 1745, 1716, 1512, 1438, 1392, 1367, 1250, 1219, 1166, 1052, 1024, and 858; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.82 (s, 1H), 5.08 (d, *J* = 7.8 Hz, 1H), 4.42 (m, 1H), 3.75 (s, 3H), 2.54−2.36 (br, m, 6H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 172.9, 155.2, 144.5, 131.6, 79.9, 52.3, 51.9, 34.0, 31.5, 28.3, 27.1; HRMS (ES) *m*/*z*: $[M + Na]^+$ calcd for $C_{13}H_{21}NO_4Na$ 278.1363; found 278.1363.

General Procedure B, Reaction of 8 with Allyl Chlorides. A flask containing CuBr·DMS (10 mol %) was placed under vacuum and heated vigorously until the gray CuBr·DMS became light green/yellow. The flask was then placed under a flow of nitrogen and allowed to cool to room temperature. This was repeated once more, and the flask was allowed to cool to room temperature. A prepared solution of **8** in DMF was transferred to the flask containing CuBr·DMS. Allylic chloride (1.5 equiv) was added, and the reaction stirred for 72 h at room temperature. The reaction mixture was then filtered through a silica plug eluting with EtOAc. The organic phase was washed with water (2 × 50 mL) and brine (50 mL). The organic phase was dried with Na_2SO_4, filtered, and the solvent removed under reduced pressure. The product was purified by flash column chromatography (EtOAc in petroleum ether (40−60) over silica).

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}hex-5-enoate 20. Synthesis was achieved by general procedure B using zinc dust (0.993 g, 15.19 mmol), iodine (11 crystals, then 5 crystals), **9** (1.665 g, 5.06 mmol), CuBr·DMS (0.064 g, 0.31 mmol), and allyl chloride (0.5 mL, 0.470 g, 6.14 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **20** as a colorless oil (1.030 g, 4.23 mmol, 84%); $[\alpha]_D^{24}$ +20.0 (*c* 1.05, $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3352, 2978, 2953, 2930, 1742, 1697, 1504, 1437, 1392, 1366, 1247, 1214, 1159, 1049, 1023, 994, 913, 858 and 778; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.80 (m, 1H), 5.04 (m, 3H), 4.34 (m, 1H), 3.75 (s, 3H), 2.12 (m, 2H), 1.92 (m, 1H), 1.73 (m, 1H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.3, 155.3, 136.9, 115.7, 79.9, 53.0, 52.3, 32.0, 29.5, 28.3; HRMS (ES) *m*/*z*: [M + Na]$^+$ calcd for $C_{12}H_{21}NO_4Na$ 266.1363; found 266.1369.

This characterization data is consistent with that previously reported.[23]

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-5-methylhex-5-enoate 21. Synthesis was achieved by general procedure B using zinc dust (1.033 g, 15.80 mmol), iodine (15 crystals, then 6 crystals), **9** (1.648 g, 5.00 mmol), CuBr·DMS (0.105 g, 0.51 mmol), and 3-chloro-2-methyl-1-propene (1.038 g, 11.46 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **21** as a colorless oil (1.009 g, 3.92 mmol, 78%); $[\alpha]_D^{24}$ +21.6 (*c* 1.11, $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3358, 2978, 2160, 1978, 1743, 1713, 1506, 1450, 1365, 1276, 1258, 1212, 1163, 1051, 1023 and 888; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.07 (d, *J* = 7.9 Hz, 1H), 4.75 (br s, 1H), 4.70 (br s, 1H), 4.33 (m, 1H), 3.75 (s, 3H), 2.09−1.88 (br m, 3H), 1.79−1.72 (br m, 4H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.3, 155.3, 144.3, 110.7, 79.9, 53.2, 52.2, 33.3, 30.7, 28.3, 22.5; HRMS (ES) *m*/*z*: [M + H]$^+$ calcd for $C_{13}H_{24}NO_4$ 258.1705; found 258.1710.

1,9-Dimethyl (2*S*,8*S*)-2,8-Bis({[(*tert*-butoxy)carbonyl]-amino})-5-methylidenenonanedioate 22. Synthesis was achieved by general procedure B using zinc dust (0.495 g, 7.57 mmol), iodine (10 crystals, then 5 crystals), **9** (0.828 g, 2.52 mmol), CuBr·DMS (0.058 g, 0.28 mmol), and 3-chloro-2-chloromethyl-1-propene (0.125 mL, 0.116 g, 0.93 mmol). Purification by flash column chromatography (25% EtOAc in petroleum ether (40−60), over silica) gave **22** as a colorless oil (0.393 g, 0.86 mmol, 92%); $[\alpha]_D^{22}$ +27.5 (*c* 1.09, $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3358, 2976, 2933, 1739, 1694, 1647, 1513, 1452, 1437, 1392, 1365, 1273, 1248, 1213, 1160, 1049, 1025, 892, and 864; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.08 (d, *J* = 8.0, 2H), 4.77 (s, 2H), 4.31−4.26 (m, 2H), 3.72 (s, 6H), 2.07−1.90 (m, 6H), 1.76−1.67 (m, 2H), 1.43 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.2, 155.3, 146.5, 110.6, 79.9, 53.1, 52.2, 31.6, 30.8, 28.3; HRMS (ES) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{39}N_2O_8$ 459.2706; found 459.2690.

General Procedure C, Radical Fluorination. The protected amino acid (1 equiv) was dissolved in MeCN (20 mL) and placed under nitrogen. The solution was cooled to 0 °C. $Fe_2(ox)_3$ (15 wt % solution) and deionized water (18 mL) were added. Selectfluor was then added followed by $NaBH_4$, which was added in two portions with ≈2 min between each addition. The reaction was stirred for 45 min at 0 °C. Conc. NH_4OH solution (4 mL) was added. The reaction mixture was stirred for 1 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried with Na_2SO_4, filtered, and the solvent removed under reduced pressure. The product was isolated by column chromatography (EtOAc in petroleum ether (40−60) mixtures over silica).

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(1-fluorocyclopentyl)propanoate 2a. Synthesis was achieved by general procedure C using **1a** (0.128 g, 0.48 mmol), $Fe_2(ox)_3{\cdot}6H_2O$ (15 wt % solution) (3.283 g, 1.02 mmol), Selectfluor (0.367 g, 1.04 mmol), and $NaBH_4$ (0.069 g, 1.82 mmol; 0.066 g, 1.74 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **2a** as a colorless oil (0.088 g, 0.30 mmol, 63%); crystals were obtained by dissolving in hot pentane and leaving the solution to slowly evaporate; mp 43−46 °C; $[\alpha]_D^{23}$ +5.0 (*c* 1.20, $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3355, 2972, 1752, 1685, 1531, 1438, 1391, 1366, 1337, 1318, 1289, 1205, 1161, 1130, 1055, 1028, 996, 960, 866, 792, 778, and 761; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.26 (d, *J* = 6.0 Hz, 1H), 4.44 (m, 1H), 3.73 (s, 3H), 2.32−1.96 (br m, 4H), 1.79 (m, 2H), 1.69−1.52 (br m, 4H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.1, 155.2, 105.9 (d, *J* = 173 Hz), 79.9, 52.3, 51.3, 39.9 (d, *J* = 23 Hz), 37.8 (d, *J* = 24 Hz), 37.7 (d, *J* = 24 Hz), 28.3, 23.6, 23.5; ^{19}F{^{1}H} NMR ($CDCl_3$, 377 MHz) δ_F −142.8 (s); HRMS (ES) *m*/*z*: [M + Na]$^+$ calcd for $C_{14}H_{24}FNO_4Na$ 312.1582; found 312.1573.

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(1-fluorocyclohexyl)propanoate 2b. Synthesis was achieved by general procedure C using **1b** (0.155 g, 0.55 mmol), $Fe_2(ox)_3{\cdot}6H_2O$ (15 wt % solution) (3.318 g, 1.03 mmol), Selectfluor (0.365 g, 1.03 mmol), and $NaBH_4$ (0.066 g, 1.74 mmol; 0.070 g, 1.85 mmol). Purification by flash column chromatography (8% EtOAc in petroleum ether (40−60), over silica) gave **2b** as a colorless oil (0.107 g, 0.35 mmol, 64%); $[\alpha]_D^{24}$ +2.0 (*c* 1.13, $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3367, 2936, 2866, 1746, 1710, 1504, 1437, 1392, 1366, 1276, 1257, 1212, 1160, 1114, 1049, 1023, 965, 946, 917, 865, and 827; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.20 (d, *J* = 4.6 Hz, 1H), 4.43 (m, 1H), 3.74 (s, 3H), 2.16−1.87 (br m, 4H), 1.64−1.24 (m, 17H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.3, 155.3, 95.7 (d, *J* = 170 Hz), 79.9, 52.4, 50.2, 41.4 (d, *J* = 22 Hz), 35.6 (d, *J* = 22 Hz), 34.7 (d, *J* = 22 Hz), 28.3, 25.1, 21.8; ^{19}F NMR ($CDCl_3$, 377 MHz) δ_F −153.7 (br s); HRMS (ES) *m*/*z*: [M + Na]$^+$ calcd for $C_{15}H_{26}FNO_4Na$ 326.1744; found 326.1736.

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(1-fluorocycloheptyl)propanoate 2c. Synthesis was achieved by general procedure C using **1c** (0.148 g, 0.50 mmol), $Fe_2(ox)_3{\cdot}6H_2O$ (15 wt % solution) (3.236 g, 1.00 mmol), Selectfluor (0.368 g, 1.04 mmol), and $NaBH_4$ (0.061 g, 1.61 mmol; 0.063 g, 1.67 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **2c** as a colorless oil (0.112 g, 0.35 mmol, 70%); $[\alpha]_D^{24}$ +1.8 (*c* 1.14, $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3362, 2931, 2858, 1744, 1712, 1502, 1458, 1438, 1389, 1365, 1252, 1204, 1159, 1050, 1022, 961, 861, and 836; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.21 (m, 1H), 4.41 (m, 1H), 3.75 (s, 3H), 1.72 (br m, 23H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.3, 155.3, 100.1 (d, *J* = 169 Hz), 80.0, 52.4, 50.6, 42.4 (d, *J* = 22 Hz), 39.2 (d, *J* = 24 Hz), 38.0 (d, *J* = 24 Hz), 29.55, 29.51, 28.3, 22.1 (d, *J* = 7 Hz), 22.0 (d, *J* = 5 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, 377 MHz) δ_F −137.7; HRMS (ES) *m*/*z*: [M + Na]$^+$ calcd for $C_{16}H_{28}FNO_4Na$ 340.1900; found 340.1913.

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(1-fluorocyclooctyl)propanoate 2d. Synthesis was achieved by general procedure C using **1d** (0.171 g, 0.55 mmol), $Fe_2(ox)_3{\cdot}6H_2O$ (15 wt % solution) (3.320 g, 1.03 mmol), Selectfluor (0.367 g, 1.04 mmol), and $NaBH_4$ (0.070 g, 1.85 mmol; 0.065 g, 1.72 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **2d** as a colorless oil (0.120 g, 0.36 mmol, 65%); $[\alpha]_D^{25}$ +3.8 (*c* 1.58, $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3363, 2921, 2857, 1747, 1713, 1504, 1475, 1436, 1391, 1366, 1276, 1248, 1213, 1160, 1048, 1026, 917, 864, and 829; ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 5.24 (d, J = 4.2 Hz, 1H), 4.40 (m, 1H), 3.74 (s, 3H), 1.71 (br m, 25H); ^{13}C NMR (CDCl$_3$, 100 MHz), δ_C 173.3, 155.3, 99.8 (d, J = 167 Hz), 79.9, 52.4, 50.6, 40.3 (d, J = 21 Hz), 34.7 (d, J = 24 Hz), 33.2 (d, J = 24 Hz), 28.3, 28.0, 27.8, 24.9, 21.9 (d, J = 8 Hz), 21.8 (d, J = 8 Hz); ^{19}F{^{1}H} NMR (CDCl$_3$, 377 MHz) δ_F −137.2; HRMS (ES) m/z: [M + Na]$^+$ calcd for $C_{17}H_{30}FNO_4Na$ 354.2057; found 354.2067.

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(4-fluorooxan-4-yl)propanoate 23. Synthesis was achieved by general procedure C using **10** (0.144 g, 0.50 mmol), Fe$_2$(ox)$_3$·6H$_2$O (15 wt % solution) (3.247 g, 1.01 mmol), Selectfluor (0.355 g, 1.00 mmol), and NaBH$_4$ (0.061 g, 1.61 mmol; 0.067 g, 1.77 mmol). Purification by flash column chromatography (15−25% EtOAc in petroleum ether (40−60), over silica) gave **23** as a colorless oil (0.090 g, 0.29 mmol, 58%); $[\alpha]_D^{24}$ +7.0 (c 1.42, CHCl$_3$); ν_{max}(ATR)/cm^{-1} 3347, 2958, 2930, 2867, 1747, 1710, 1513, 1436, 1392, 1366, 1280, 1249, 1214, 1160, 1102, 1048, 1014, 985, 838, 780, and 758; ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 5.17 (d, J = 6.7 Hz, 1H), 4.50 (m, 1H), 3.65−3.69 (m, 7H), 2.23−1.62 (m, 6H), 1.46 (s, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz), δ_C 173.0, 155.2, 92.7 (d, J = 172 Hz), 80.1, 63.4, 52.5, 49.7, 41.9 (d, J = 21 Hz), 35.6 (d, J = 22 Hz), 35.1 (d, J = 22 Hz), 28.3; ^{19}F{^{1}H} NMR (CDCl$_3$, 377 MHz) δ_F −159.8; HRMS (ES) m/z: [M + Na]$^+$ calcd for $C_{14}H_{24}FNO_5Na$ 328.1536; found 328.1551.

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(1,4,4-trifluorocyclohexyl)propanoate 24. Synthesis was achieved by general procedure C with the modifications discussed in the Results and Discussion section using **11** (0.161 g, 0.50 mmol), Fe$_2$(ox)$_3$·6H$_2$O (15 wt % solution) (3.289 g, 1.02 mmol), Selectfluor (0.905 g, 2.55 mmol), and NaBH$_4$ (0.305 g, 8.06 mmol) in 0.1 M NaOH solution (30 mL) added over 6 h. Purification by flash column chromatography (13% EtOAc in petroleum ether (40−60), over silica) gave the product as a colorless oil that solidified on standing to give **24** as a white solid. Recrystallized from hot pentane (0.110 g, 0.32 mmol, 64%); mp 67−69 °C; $[\alpha]_D^{24}$ +1.9 (c 1.03, CHCl$_3$); ν_{max}(ATR)/cm^{-1} 3378, 3010, 2970, 2936, 2862, 2339, 1763, 1689, 1530, 1442, 1389, 1367, 1343, 1316, 1270, 1256, 1221, 1162, 1122, 1095, 1053, 1022, 992, 963, 913, 893, 865, and 844; ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 5.16 (d, J = 7.5 Hz, 1H), 4.48 (m, 1H), 3.76 (s, 3H), 2.20−2.00 (br m, 8H), 1.82−1.65 (br m, 2H), 1.45 (s, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz), δ_C 172.9, 155.2, 122.6 (dd, J = 243 Hz, 238 Hz), 93.5 (d, J = 173 Hz), 80.2, 52.6, 50.1, 41.3 (d, J = 21 Hz), 31.8 (dd, J = 10 Hz, 10 Hz), 31.5 (dd, J = 10 Hz, 10 Hz), 29.2 (apparent t, J = 25 Hz), 28.3; ^{19}F{^{1}H} NMR (CDCl$_3$, 377 MHz) δ_F −93.4 (d, J = 238 Hz, 1 F), −105.0 (d, J = 238 Hz, 1 F), −162.6 (s, 1 F); HRMS (ES) m/z: [M + Na]$^+$ calcd for $C_{15}H_{24}F_3NO_4Na$ 362.1555; found 362.1541.

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-fluoro-4-methylpentanoate 25. Synthesis was achieved by general procedure C using **16** (0.119 g, 0.49 mmol), Fe$_2$(ox)$_3$·6H$_2$O (15 wt % solution) (3.247 g, 1.01 mmol), Selectfluor (0.357 g, 1.01 mmol), and NaBH$_4$ (0.066 g, 1.74 mmol; 0.059 g, 1.56 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **25** as a colorless oil, which solidified on standing (0.107 g, 0.41 mmol, 84%); mp 37−40 °C; $[\alpha]_D^{24}$ −2.5 (c 1.18, CHCl$_3$); ν_{max}(ATR)/cm^{-1} 3373, 2980, 2957, 2917, 2849, 1746, 1712, 1505, 1438, 1390, 1366, 1249, 1206, 1161, 1049, 1027, 990, 889, 866, 849, 797, and 781; ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 5.20 (d, J = 6.2 Hz, 1H), 4.41 (m, 1H), 3.73 (s, 3H), 2.17−1.94 (br m, 2H), 1.43 (s, 9H), 1.41 (d, J = 21.5 Hz, 6H); ^{13}C NMR (CDCl$_3$, 100 MHz), δ_C 173.1, 155.3, 95.0 (d, J = 166 Hz), 80.0, 52.4, 50.8, 42.6 (d, J = 22 Hz), 28.3, 27.1 (d, J = 25 Hz), 26.5 (d, J = 25 Hz); ^{19}F{^{1}H} NMR (CDCl$_3$, 377 MHz) δ_F −136.6 (s); HRMS (ES) m/z: [M + Na]$^+$ calcd for $C_{12}H_{22}FNO_4Na$ 286.1425; found 286.1427.

Methyl (2*R*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-fluoro-4-methylpentanoate *ent*-25. Synthesis was achieved by general procedure C using ***ent*-16** (0.124 g, 0.51 mmol), Fe$_2$(ox)$_3$·6H$_2$O (15 wt % solution) (3.330 g, 1.03 mmol), Selectfluor (0.379 g, 1.07 mmol), and NaBH$_4$ (0.058 g, 1.54 mmol; 0.064 g, 1.69 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave ***ent*-25** as a colorless oil, which solidified on standing (0.118 g, 0.45 mmol, 88%); mp 38−40 °C; $[\alpha]_D^{24}$ +3.1 (c 1.31, CHCl$_3$).

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-5-fluoro-5-methylhexanoate 26. Synthesis was achieved by general procedure C using **17** (0.130 g, 0.51 mmol), Fe$_2$(ox)$_3$·6H$_2$O (15 wt % solution) (3.109 g, 0.96 mmol), Selectfluor (0.368 g, 1.04 mmol), and NaBH$_4$ (0.064 g, 1.70 mmol; 0.061 g, 1.60 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **26** as a colorless oil (0.104 g, 0.38 mmol, 75%); $[\alpha]_D^{24}$ +14.0 (c 1.07, CHCl$_3$); ν_{max}(ATR)/cm^{-1} 3358, 3004, 2980, 2933, 1743, 1712, 1512, 1454, 1438, 1389, 1366, 1276, 1260, 1210, 1160, 1053, 1027, and 875; ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 5.08 (d, J = 8.0 Hz, 1H), 4.30 (m, 1H), 3.75 (s, 3H), 2.00−1.91 (br m, 1H), 1.78−1.59 (br m, 3H), 1.43 (s, 9H), 1.34 (d, J = 21.3 Hz, 6H); ^{13}C NMR (CDCl$_3$, 100 MHz), δ_C 173.1, 155.4, 94.9 (d, J = 166 Hz), 79.9, 53.3, 52.3, 36.78 (d, J = 23 Hz), 28.3, 27.14 (d, J = 5 Hz), 26.7 (d, J = 24 Hz), 26.5 (d, J = 24 Hz); ^{19}F{^{1}H} NMR (CDCl$_3$, 377 MHz) δ_F −139.5 (s); HRMS (ES) m/z: [M + H]$^+$ calcd for $C_{13}H_{24}FNO_4$ 278.1768; found 278.1756.

Synthesis of **26** was also achieved by general procedure C using **21** (0.133 g, 0.52 mmol), Fe$_2$(ox)$_3$·6H$_2$O (15 wt % solution) (3.285 g, 1.02 mmol), Selectfluor (0.358 g, 1.01 mmol), and NaBH$_4$ (0.067 g, 1.77 mmol; 0.067 g, 1.77 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **26** as a colorless oil (0.090 g, 0.32 mmol, 62%), identical to that isolated above.

Methyl (2*S*,4*RS*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-fluoro-4-methylhexanoate 27. Synthesis was achieved by general procedure C using **(*E*/*Z*)-18** (7:1, E/Z) (0.132 g, 0.51 mmol), Fe$_2$(ox)$_3$·6H$_2$O (15 wt % solution) (3.460 g, 1.07 mmol), Selectfluor (0.358 g, 1.01 mmol), and NaBH$_4$ (0.062 g, 1.64 mmol; 0.061 g, 1.61 mmol). Purification by flash column chromatography (8% EtOAc in petroleum ether (40−60), over silica) gave **27** as a colorless oil as a mixture of diastereomers (0.114 g, 0.41 mmol, 80%); ν_{max}(thin film, NaCl plates)/cm^{-1} 3371, 2979, 2937, 2889, 1750, 1716, 1513, 1456, 1438, 1386, 1367, 1280, 1249, 1208, 1167, 1056, 1026, 865, and 781; ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 5.19 (m, 1H), 4.40 (m, 1H), 3.73 (s, 3H), 2.01 (m, 2H), 1.66 (m, 2H), 1.43 (s, 9H), 1.36 (d, J = 21.9 Hz, 3H), 0.93 (td, J = 7.5 Hz, 1.4 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz), δ_C 173.2, 155.3, 97.2 (d, J = 168 Hz), 97.1 (d, J = 168 Hz), 79.9, 52.4, 50.6 (d, J = 24 Hz), 40.8 (d, J = 22 Hz), 40.3 (d, J = 22 Hz), 33.1 (d, J = 23 Hz), 32.3 (d, J = 23 Hz), 28.3, 23.7 (d, J = 25 Hz), 23.2 (d, J = 25 Hz), 8.0 (d, J = 7 Hz), 7.8 (d, J = 7 Hz); ^{19}F{^{1}H} NMR (CDCl$_3$, 377 MHz) δ_F −144.3 (s), −144.6 (s); HRMS (ES) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{24}FNO_4Na$ 300.1582; found 300.1586.

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(1-fluorocyclobutyl)propanoate 28. Synthesis was achieved by general procedure C using **19** (0.135 g, 0.53 mmol), $Fe_2(ox)_3 \cdot 6H_2O$ (15 wt % solution) (3.289 g, 1.02 mmol), Selectfluor (0.378 g, 1.07 mmol), and $NaBH_4$ (0.068 g, 1.80 mmol; 0.066 g, 1.74 mmol). Purification by flash column chromatography (8% EtOAc in petroleum ether (40−60), over silica) gave **28** as a colorless oil, which solidifies on standing (0.118 g, 0.43 mmol, 81%); mp 52−54 °C; $[\alpha]_D^{25}$ +7.6 (*c* 1.19, $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3362, 2982, 2941, 1755, 1686, 1510, 1457, 1440, 1393, 1365, 1291, 1250, 1219, 1158, 1124, 1093, 1048, 1021, 980, 949, 909, 862, 874, 790, 777, and 758; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.22 (d, *J* = 7.0 Hz, 1H), 4.43 (m, 1H), 3.73 (s, 3H), 2.39−2.13 (m, 6H), 1.91−1.82 (m, 1H), 1.60−1.52 (m, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.0, 155.2, 96.8 (d, *J* = 210 Hz), 79.9, 52.4, 50.5, 38.7 (d, *J* = 22 Hz), 33.9 (d, *J* = 22 Hz), 33.7 (d, *J* = 22 Hz), 28.3, 12.1 (d, *J* = 12 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, 377 MHz) δ_F −132.3 (s); HRMS (ES) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{22}FNO_4Na$ 298.1425; found 298.1425.

Methyl (2*S*,5*RS*)-2-{[(*tert*-Butoxy)carbonyl]amino}-5-fluorohexanoate 29. Synthesis was achieved by general procedure C using **20** (0.123 g, 0.51 mmol), $Fe_2(ox)_3 \cdot 6H_2O$ (15 wt % solution) (3.253 g, 1.01 mmol), Selectfluor (0.363 g, 1.02 mmol), and $NaBH_4$ (0.064 g, 1.69 mmol; 0.061 g, 1.61 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **29** as a colorless oil as a mixture of diastereomers (0.097 g, 0.37 mmol, 73%); $[\alpha]_D^{24}$ +10.0 (*c* 1.75, $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3346, 2978, 2933, 1743, 1705, 1508, 1451, 1391, 1366, 1296, 1247, 1214, 1159, 1049, 1020, 923, 838, and 780; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.09 (d, *J* = 6.6 Hz, 1H), 4.76−4.54 (br m, 1H), 4.32 (m, 1H), 3.74 (s, 3H), 2.07−1.51 (br, m, 4H), 1.44 (s, 9H), 1.32 (dd, *J* = 23.9 Hz, 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.1, 155.4, 90.0 (d, *J* = 165 Hz), 90.3 (d, *J* = 166 Hz), 79.9, 53.2, 52.9, 52.33, 52.31, 32.7 (d, *J* = 21 Hz), 32.6 (d, *J* = 21 Hz), 28.4 (d, *J* = 4 Hz) 28.3, 21.0 (d, *J* = 23 Hz), 20.9 (d, *J* = 23 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, 377 MHz) δ_F −173.7 (s), −174.1 (s); HRMS (ES) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{23}FNO_4$ 264.1611; found 264.1621.

1,9-Dimethyl (2*S*,8*S*)-2,8-Bis({[(*tert*-butoxy)carbonyl]-amino})-5-fluoro-5-methylnonane-dioate 30. Synthesis was achieved by general procedure C using **22** (0.251 g, 0.55 mmol), $Fe_2(ox)_3 \cdot 6H_2O$ (15 wt % solution) (3.231 g, 1.00 mmol), Selectfluor (0.361 g, 1.02 mmol), and $NaBH_4$ (0.065 g, 1.72 mmol; 0.064 g, 1.69 mmol). Purification by flash column chromatography (20% EtOAc in petroleum ether (40−60), over silica) gave **30** as a colorless oil (0.237 g, 0.50 mmol, 91%); $[\alpha]_D^{25}$ +17.8 (*c* 1.01, $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3358, 2978, 2937, 2159, 2031, 1978, 1740, 1694, 1514, 1454, 1438, 1392, 1365, 1276, 1255, 1211, 1158, 1049, 1024, 881, and 856; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.10 (d, *J* = 8.1 Hz, 2H), 4.29 (m, 2H), 3.74 (s, 6H), 1.91 (br m, 2H), 1.63 (br m, 6H), 1.44 (s, 18H), 1.27 (d, *J* = 21.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.0, 155.4, 95.9 (d, *J* = 170 Hz), 80.0, 53.3, 52.4, 35.2 (d, *J* = 23 Hz), 35.0 (d, *J* = 23 Hz), 28.3, 26.82 (d, *J* = 6 Hz), 26.76 (d, *J* = 6 Hz), 23.9 (d, *J* = 25 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, 377 MHz) δ_F −147.1 (s); HRMS (ES) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{40}FN_2O_8$ 479.2769; found 479.2774.

General Procedure D, NHBoc Deprotection. The Boc-protected amino acid was dissolved in CH_2Cl_2 (3 mL), TFA (3 mL) was added, and the solution was stirred overnight. The mixture was concentrated under reduced pressure and the residue redissolved in 1:1 toluene/MeOH (6 mL), which was removed under reduced pressure; this process was repeated twice more to afford the product as the TFA salt without further purification.

Methyl (2*S*,4*RS*)-2-Ammonium-4-fluoro-4-methylhexanoate Trifluoroacetate 31. Synthesis was achieved by general procedure D using **27** (0.030 g, 0.11 mmol), CH_2Cl_2/TFA (1:1, 6 mL) and isolated without further purification gave **31** as a colorless oil as a mixture of diastereomers (0.031 g, 0.11 mmol, >99%); ν_{max}(thin film, NaCl plates)/cm^{-1} 3445, 2962, 2666, 1751, 1675, 1631, 1533, 1441, 1384, 1240, 1203, 1138, 1034, 927, 838, and 800; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.42 (br s, 3H), 4.78−4.58 (br m, 1H), 4.07−4.00 (br m, 1H), 3.82 (s, 3H), 2.19−1.68 (br m, 4H), 1.34 (dd, *J* = 24.0 Hz, 5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 169.9, 162.3 (q, *J* = 36.8 Hz), 90.2 (d, *J* = 165.6 Hz), 89.9 (d, *J* = 165.7 Hz), 53.3, 52.9, 52.7, 32.0 (d, *J* = 21.3 Hz), 31.6 (d, *J* = 21.1 Hz), 26.4 (d, *J* = 3.8 Hz), 26.1 (d, *J* = 3.8 Hz), 20.6 (d, *J* = 22.4 Hz), 20.5 (d, *J* = 22.4 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, 377 MHz) δ_F −76.0 (s, 3 F), −174.6 (s, 0.46 F), −175.0 (s, 0.49 F); ^{19}F NMR ($CDCl_3$, 377 MHz) δ_F −76.0 (s, 3 F), −174.7 (m, 0.98 F); HRMS (ES) *m/z*: $[M + H]^+$ calcd for $C_7H_{15}FNO_2$ 164.1081; found 164.1081.

Methyl (2*S*,5*RS*)-2-Ammonium-5-fluorohexanoate Trifluoroacetate 32. Synthesis was achieved by general procedure D using **29** (0.019 g, 0.07 mmol), CH_2Cl_2/TFA (1:1, 6 mL) and isolated without further purification gave **32** as a colorless oil as a mixture of diastereomers (0.020 g, 0.07 mmol, 96%); ν_{max}(thin film, NaCl plates)/cm^{-1} 3423, 2980, 1754, 1678, 1533, 1442, 1385, 1299, 1237, 1204, 1137, 1055, 997, 949, 886, 838, and 801; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.39 (br m, 3H), 4.26 (m, 1H), 3.81 (s, 3H), 2.44−2.14 (m, 2H), 1.84−1.59 (m, 2H), 1.42 (d, *J* = 22.0 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 169.9, 169.7, 97.9 (d, *J* = 166.6 Hz), 97.6 (d, *J* = 166.8 Hz), 53.5, 53.4, 50.0, 49.8, 38.9 (d, *J* = 20.8 Hz), 38.8 (d, *J* = 20.5 Hz), 33.2 (d, *J* = 23.0 Hz), 31.6 (d, *J* = 23.4 Hz), 23.6 (d, *J* = 24.2 Hz), 22.5 (d, *J* = 24.8 Hz), 7.8 (d, *J* = 7.9 Hz), 7.6 (d, *J* = 7.3 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, 377 MHz) δ_F −75.8 (s, 3 F), −146.0 (s, 0.5 F), −147.4 (s, 0.48 F); ^{19}F NMR ($CDCl_3$, 377 MHz) δ_F −75.8 (s, 3 F), −146.1 (m, 0.49 F), −147.4 (m, 0.47 F); HRMS (ES) *m/z*: $[M + H]^+$ calcd for $C_8H_{16}FNO_2$ 178.1238; found 178.1240.

General Procedure E, Radical Hydroazidation. The protected unsaturated amino acid was dissolved in MeCN (20 mL), and the solution was cooled to 0 °C. $Fe_2(ox)_3 \cdot 6H_2O$ (15 wt % solution) was added followed by deionized water (18 mL), NaN_3 was then added followed by $NaBH_4$, which was added in eight portions with ≈2 min between each addition. The reaction was stirred for 45 min at 0 °C. Conc. NH_4OH solution (30 mL) was added. The reaction mixture was stirred for 1 min. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried with Na_2SO_4, filtered, and the solvent removed under reduced pressure. The product was purified by flash column chromatography (EtOAc in petroleum ether (40−60) mixtures over silica).

Methyl (2*S*)-4-Azido-2-{[(*tert*-butoxy)carbonyl]-amino}-4-methylpentanoate 33. Synthesis was achieved by general procedure E using **16** (0.127 g, 0.52 mmol), $Fe_2(ox)_3 \cdot 6H_2O$ (15 wt % solution) (7.698 g, 2.39 mmol), NaN_3 (0.125 g, 1.92 mmol), and $NaBH_4$ (0.066 g, 1.74 mmol;

0.078 g, 2.06 mmol; 0.067 g, 1.77 mmol; 0.073 g, 1.93 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **33** as a colorless oil (0.133 g, 0.46 mmol, 88%); $[\alpha]_D^{24}$ +11.6 (*c* 0.86, $CHCl_3$); ν_{max}(thin film, NaCl plates)/cm^{-1} 3364, 2978, 2932, 2851, 2100, 1747, 1716, 1512, 1456, 1438, 1392, 1368, 1252, 1218, 1167, 1051, 1028, 994, 863, and 760; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.21 (d, *J* = 7.7 Hz, 1H), 4.40 (m, 1H), 3.74 (s, 3H), 1.97 (dd, *J* = 14.5 Hz, 4.4 Hz, 1H), 1.78 (dd, *J* = 14.5 Hz, 8.4 Hz, 1H), 1.43 (s, 9H), 1.36 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.1, 155.2, 80.1, 60.3, 52.4, 50.9, 43.0, 28.3, 26.3, 26.0; HRMS (ES) *m*/*z*: [M + Na]$^+$ calcd for $C_{12}H_{22}N_4O_4Na$ 309.1533; found 309.1536.

Methyl (2*S*)-3-(1-Azidocyclopentyl)-2-{[(*tert*-butoxy)-carbonyl]amino}propanoate 34. Synthesis was achieved by general procedure E using **1a** (0.141 g, 0.52 mmol), $Fe_2(ox)_3{\cdot}6H_2O$ (15 wt % solution) (7.371 g, 2.37 mmol), NaN_3 (0.109 g, 1.68 mmol), and $NaBH_4$ (0.071 g, 1.77 mmol; 0.065 g, 1.72 mmol; 0.066 g, 1.74 mmol, 0.071 g, 1.88 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **34** as a colorless oil (0.107 g, 0.34 mmol, 65%); $[\alpha]_D^{25}$ +15.1 (*c* 1.33, $CHCl_3$); ν_{max}(thin film, NaCl plates)/cm^{-1} 3364, 2968, 2919, 2880, 2102, 1748, 1717, 1513, 1451, 1438, 1393, 1367, 1254, 1208, 1166, 1055, 1023, 864, and 779; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.21 (d, *J* = 7.6 Hz, 1H), 4.44 (m, 1H), 3.75 (s, 3H), 2.18 (dd, *J* = 14.6 Hz, 4.9 Hz, 1H), 1.98 (dd, *J* = 14.3, *J* = 7.2 Hz, 1H), 1.92 (m, 2H), 1.82−1.66 (br m, 4H), 1.65−1.54 (br m, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.1, 155.1, 80.0, 71.7, 52.5, 51.5, 40.8, 37.3, 37.2, 28.3, 23.4, 23.3; HRMS (ES) *m*/*z*: [M + Na]$^+$ calcd for $C_{14}H_{24}N_4O_4Na$ 335.1690; found 335.1688.

Methyl (2*S*)-3-(1-Azidocyclohexyl)-2-{[(*tert*-butoxy)-carbonyl]amino}propanoate 35. Synthesis was achieved by general procedure E using **1b** (0.142 g, 0.50 mmol), $Fe_2(ox)_3{\cdot}6H_2O$ (15 wt % solution) (7.371 g, 2.29 mmol), NaN_3 (0.145 g, 2.23 mmol), and $NaBH_4$ (0.068 g, 1.80 mmol; 0.059 g, 1.56 mmol; 0.075 g, 1.98 mmol, 0.070 g, 1.85 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **35** as a colorless oil (0.116 g, 0.36 mmol, 72%); $[\alpha]_D^{24}$ +4.4 (*c* 1.59, $CHCl_3$); ν_{max}(thin film, NaCl plates)/cm^{-1} 3363, 2977, 2934, 2861, 2103, 1747, 1717, 1513, 1450, 1438, 1390, 1367, 1254, 1211, 1164, 1051, 1024, 864, and 779; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.18 (d, *J* = 7.8 Hz, 1H), 4.42 (m, 1H), 3.74 (s, 3H), 2.06 (dd, *J* = 14.8 Hz, 4.5 Hz, 1H), 1.83 (dd, *J* = 14.8 Hz, 8.1 Hz, 1H), 1.72 (m, 2H), 1.59−1.24 (br m, 17H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.2, 155.1, 80.0, 62.8, 52.5, 50.2, 41.5, 34.8, 34.3, 28.3, 25.1, 22.0; HRMS (ES) *m*/*z*: [M + Na]$^+$ calcd for $C_{15}H_{26}N_4O_4Na$ 349.1846; found 349.1851.

Methyl (2*S*)-5-Azido-2-{[(*tert*-butoxy)carbonyl]-amino}-5-methylhexanoate 36. Synthesis was achieved by general procedure E using **21** (0.134 g, 0.52 mmol), $Fe_2(ox)_3{\cdot}6H_2O$ (15 wt % solution) (7.585 g, 2.35 mmol), NaN_3 (0.130 g, 2.00 mmol), and $NaBH_4$ (0.061 g, 1.61 mmol; 0.074 g, 1.96 mmol; 0.066 g, 1.74 mmol; 0.076 g, 2.01 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave the product **36** as a colorless oil (0.108 g, 0.36 mmol, 69%); $[\alpha]_D^{24}$ +17.4 (*c* 1.09, $CHCl_3$); ν_{max}(thin film, NaCl plates)/cm^{-1} 3359, 2977, 2935, 2098, 1745, 1718, 1512, 1454, 1440, 1392, 1368, 1255, 1209, 1166, 1056, 1029, 867, 853, and 780; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.11 (d, *J* = 7.9 Hz, 1H), 4.29 (m, 1H), 3.74 (s, 3H), 1.91 (br m, 1H), 1.68 (br m, 1H), 1.53 (br m, 2H), 1.43 (s, 9H), 1.25 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.0, 155.3, 79.9, 61.0, 53.3, 52.4, 36.8, 28.3, 27.5, 26.0, 25.8; HRMS (ES) *m*/*z*: [M + Na]$^+$ calcd for $C_{13}H_{24}N_4O_4Na$ 323.1690; found 323.1692.

Synthesis of **36** was also achieved by general procedure E using **17** (0.128 g, 0.50 mmol), $Fe_2(ox)_3{\cdot}6H_2O$ (15 wt % solution) (6.733 g, 2.09 mmol), NaN_3 (0.125 g, 1.92 mmol), and $NaBH_4$ (0.066 g, 1.74 mmol; 0.058 g, 1.53 mmol; 0.060 g, 1.59 mmol; 0.066 g, 1.74 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **36** as a colorless oil (0.130 g, 0.43 mmol, 86%), identical to that isolated above.

Methyl (2*S*,4*RS*)-4-Azido-2-{[(*tert*-butoxy)carbonyl]-amino}-4-methylhexanoate 37. Synthesis was achieved by general procedure E using **(*E*/*Z*)-18** (7:1, E/Z) (0.131 g, 0.51 mmol), $Fe_2(ox)_3{\cdot}6H_2O$ (15 wt % solution) (7.627 g, 2.37 mmol), NaN_3 (0.126 g, 1.94 mmol), and $NaBH_4$ (0.060 g, 1.59 mmol; 0.074 g, 1.96 mmol; 0.075 g, 1.98 mmol; 0.078 g, 2.06 mmol). Purification by flash column chromatography (10% EtOAc in petroleum ether (40−60), over silica) gave **37** as a colorless oil, which is a mixture of diastereomers (0.096 g, 0.32 mmol, 63%); ν_{max}(thin film, NaCl plates)/cm^{-1} 3361, 2977, 2935, 2883, 2105, 1748, 1716, 1514, 1458, 1437, 1390, 1367, 1255, 1205, 1166, 1056, 1025, 862, and 779; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.20 (d, *J* = 7.8 Hz, 1H), 4.39 (m, 1H), 3.75 (s, 3H), 1.95 (m, 1H), 1.76 (m, 1H), 1.65 (m, 2H), 1.44 (s, 9H), 1.33 (s, 3H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.2, 155.2, 80.1, 63.1, 52.5, 50.7, 50.6, 41.0, 40.5, 32.8, 32.4, 28.3, 22.6, 22.4, 8.4, 8.3; HRMS (ES) *m*/*z*: [M + H]$^+$ calcd for $C_{13}H_{25}N_4O_4$ 301.1870; found 301.1872.

General Procedure F, Azide Reduction. The azido amino acid was dissolved in EtOAc, 10 wt % Pd on carbon was added (≈20 wt %), and the mixture was stirred overnight under an atmosphere of hydrogen. The product was purified by flash column chromatography (EtOAc in petroleum ether (40−60) mixtures over silica).

***tert*-Butyl *N*-[(3*S*)-5,5-Dimethyl-2-oxopyrrolidin-3-yl]-carbamate 38.** Synthesis was achieved by general procedure F using **33** (0.138 g, 0.48 mmol), EtOAc (4 mL), Pd/C 10 wt % (0.037 g, ≈20 wt %). Purification by flash column chromatography (50% EtOAc in petroleum ether (40−60), over silica) gave **38** as a white solid (0.109 g, 0.48 mmol, >99%); mp 121−123 °C; $[\alpha]_D^{25}$ +27.4 (*c* 1.09, $CHCl_3$); ν_{max}(thin film, NaCl plates)/cm^{-1} 3284, 2975, 2933, 2883, 1705, 1528, 1455, 1420, 1392, 1368, 1327, 1292, 1247, 1169, 1056, 1028, 1001, 979, 885, 835, and 755; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.11 (br s, 1H), 5.24 (br d, *J* = 4.3 Hz, 1H), 4.35 (br m, 1H), 2.54 (br t, *J* = 8.3 Hz, 1H), 1.75 (br t, *J* = 11.1 Hz, 1H), 1.43 (s, 9H), 1.31 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 174.2, 155.9, 79.8, 53.9, 52.1, 44.2, 29.9, 28.5, 28.3; HRMS (ES) *m*/*z*: [M + Na]$^+$ calcd for $C_{11}H_{20}N_2O_3Na$ 251.1366; found 251.1366.

***tert*-Butyl *N*-[(3*S*)-2-Oxo-1-azaspiro[4.4]nonan-3-yl]-carbamate 39.** Synthesis was achieved by general procedure F using **34** (0.161 g, 0.52 mmol), EtOAc (4 mL), Pd/C 10 wt % (0.038 g, ≈20 wt %). Purification by flash column chromatography (50% EtOAc in petroleum ether (40−60), over silica) gave **39** as a colorless oil (0.121 g, 0.48 mmol, 92%); $[\alpha]_D^{25}$ +13.9 (*c* 1.22, $CHCl_3$); ν_{max}(thin film, NaCl plates)/cm^{-1} 3276, 2967, 2874, 1702, 1523, 1454, 1391, 1366, 1323, 1285, 1248, 1168, 1062, 1028, 1007, 839, and 753; ^{1}H

NMR ($CDCl_3$, 400 MHz) δ_H 7.57 (br s, 1H), 5.28 (br s, 1H), 4.29 (m, 1H), 2.61 (br t, J = 9.4 Hz, 1H), 1.86−1.63 (br m, 9H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 174.6, 160.0, 79.7, 64.0, 52.2, 42.8, 39.4, 38.4, 28.3, 23.5, 22.7; HRMS (ES) m/z: $[M + Na]^+$ calcd for $C_{13}H_{22}N_2O_3Na$ 277.1523; found 277.1525.

***tert*-Butyl *N*-[(3*S*)-2-Oxo-1-azaspiro[4.5]decan-3-yl]-carbamate 40.** Synthesis was achieved by general procedure F using **35** (0.106 g, 0.32 mmol), EtOAc (5 mL), Pd/C 10 wt % (0.023 g, ≈20 wt %). Purification by flash column chromatography (40% EtOAc in petroleum ether (40−60), over silica) gave a colorless oil that solidified on standing. Recrystallization from hot Et_2O/pentane (1:1) gave compound **40** (0.079 g, 0.29 mmol, 91%); mp 160−163 °C; $[\alpha]_D^{24}$ +24.1 (c 1.14, $CHCl_3$); ν_{max}(thin film, NaCl plates)/cm^{-1} 3231, 3029, 3006, 2978, 2932, 2857, 1702, 1501, 1453, 1391, 1366, 1332, 1293, 1280, 1246, 1170, 1064, 973, 854, and 760; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.49 (br s, 1H), 5.24 (br s, 1H), 4.29 (br m, 1H), 2.67 (br t, J = 9.7 Hz, 1H), 1.62−1.49 (br m, 11H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 174.3, 156.0, 79.8, 56.8, 51.5, 41.7, 39.4, 37.3, 28.3, 25.0, 23.0, 22.7; HRMS (ES) m/z: $[M + Na]^+$ calcd for $C_{14}H_{24}N_2O_3Na$ 291.1679; found 291.1679.

***tert*-Butyl *N*-[(3*S*)-6,6-Dimethyl-2-oxopiperidin-3-yl]-carbamate 41.** Synthesis was achieved by general procedure F using **36** (0.180 g, 0.60 mmol), EtOAc (3 mL), Pd/C 10 wt % (0.037 g, ≈20 wt %). Purification by flash column chromatography (50% EtOAc in petroleum ether (40−60), over silica) gave compound **41** as a white solid (0.144 g, 0.59 mmol, 98%); mp 124−127 °C; $[\alpha]_D^{25}$ +47.8 (c 1.36, $CHCl_3$); ν_{max}(thin film, NaCl plates)/cm^{-1} 3285, 3230, 2974, 2935, 1705, 1665, 1490, 1459, 1416, 1367, 1344, 1312, 1249, 1164, 1076, 1054, 1024, 971, 831, and 756; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.82 (br s, 1H), 5.46 (br s, 1H), 3.96 (m, 1H), 2.40 (m, 1H), 1.75 (m, 3H), 1.46 (s, 9H), 1.29 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 170.8, 156.0, 79.4, 53.1, 51.4, 34.4, 31.6, 29.7, 28.3, 25.3; HRMS (ES) m/z: $[M + H]^+$ calcd for $C_{12}H_{23}N_2O_3$ 243.1705; found 243.1703.

General Procedure G, Radical Hydroxylation. The amino acid was dissolved in MeCN (20 mL), and $Fe_2(ox)_3$ (15 wt % solution) and deionized water (18 mL) were added. The mixture was stirred, and a flow of air passed through the solution. $NaBH_4$ was added in eight portions with ≈2 min between each addition. The reaction mixture was then stirred for 45 min. Conc. NH_4OH solution (4 mL) was added, and the reaction mixture stirred for 1 min. The aqueous phase was extracted with 5% MeOH in CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by flash column chromatography (EtOAc in petroleum ether (40−60) mixtures over silica).

***tert*-Butyl *N*-[(3*S*)-5,5-Dimethyl-2-oxooxolan-3-yl]-carbamate 42.** Synthesis was achieved by general procedure G using **16** (0.133 g, 0.55 mmol), $Fe_2(ox)_3 \cdot 6H_2O$ (15 wt % solution) (7.701 g, 2.39 mmol), and $NaBH_4$ (0.027 g, 0.71 mmol; 0.0306 g, 0.81 mmol; 0.0228 g, 0.60 mmol; 0.039 g, 1.03 mmol; 0.031 g, 0.82 mmol; 0.036 g, 0.95 mmol; 0.025 g, 0.66 mmol; 0.037 g, 0.98 mmol). Purification by flash column chromatography (15−30% EtOAc in petroleum ether (40−60), over silica) gave **42** as a white solid (0.055 g, 0.24 mmol, 44%); mp 110−113 °C; $[\alpha]_D^{24}$ +20.0 (c 0.95, $CHCl_3$); ν_{max}(thin film, NaCl plates)/cm^{-1} 3317, 2981, 2937, 1759, 1708, 1531, 1453, 1375, 1368, 1307, 1272, 1249, 1207, 1158, 1109, 1001, 973, 952, 923, 885, and 809; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.12 (br s, 1H), 4.57 (br m, 1H), 2.67 (apparent t, J = 10.2 Hz, 1H), 1.97 (apparent t, J = 11.9 Hz, 1H), 1.50 (s, 3H), 1.46 (s, 9H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 174.6, 155.5, 82.4, 80.5, 51.3, 42.6, 29.0, 28.3, 26.9; HRMS (ES) m/z: $[M + Na]^+$ calcd for $C_{11}H_{19}NO_4Na$ 252.1206; found 252.1209.

Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-5-hydroxy-5-methylhexanoate 43. Synthesis was achieved by general procedure G using **17** (0.149 g, 0.58 mmol), $Fe_2(ox)_3 \cdot 6H_2O$ (15 wt % solution) (7.117 g, 2.21 mmol), and $NaBH_4$ (0.031 g, 0.82 mmol; 0.035 g, 0.93 mmol; 0.031 g, 0.82 mmol; 0.032 g, 0.85 mmol; 0.032 g, 0.85 mmol; 0.039 g, 1.03 mmol; 0.038 g, 1.00 mmol; 0.027 g, 0.71 mmol). Purification by flash column chromatography (30−100% EtOAc in petroleum ether (40−60), over silica) gave **43** as a colorless oil (0.099 g, 0.36 mmol, 62%); $[\alpha]_D^{24}$ +10.1 (c 1.09, $CHCl_3$); ν_{max}(thin film, NaCl plates)/cm^{-1} 3439, 3373, 2975, 2934, 1738, 1712, 1521, 1455, 1437, 1392, 1367, 1273, 1252, 1208, 1165, 1054, 1028, 914, and 858; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.20 (br m, 1H), 4.32 (br m, 1H), 3.74 (s, 3H), 1.98−1.67 (br m, 3H), 1.55−1.44 (br m, 11H), 1.21 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C 173.4, 155.4, 79.9, 70.4, 53.6, 52.3, 38.8, 29.4, 29.2, 28.3, 27.6; HRMS (ES) m/z: $[M + Na]^+$ calcd for $C_{13}H_{25}NO_5Na$ 298.1625; found 298.1626.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b01509.

Details for the X-ray structure determinations of compounds **2a**, **24**, and **40**; ^1H and ^{13}C NMR spectra for all compounds; ^{19}F NMR spectra for compounds containing fluorine; chiral HPLC traces for compounds **25** and ***ent*-25** (PDF)

Crystallographic data file (CIF)

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Notes

The authors declare no competing financial interest.

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