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Fluorination-Free Synthesis of a 4,4-Difluoro-3,3-Dimethylproline Derivative

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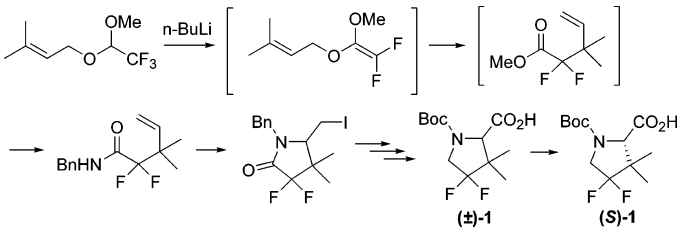


A Claisen rearrangement/iodolactamization sequence starting from commercially available trifluoroacetaldehyde methyl hemiacetal, followed by a classical chemical resolution, provided enantiomerically pure 4,4-difluoro-3,3-dimethylproline **(***S***)-1**. No hazardous fluorination reagents were used, and the overall yield over 12 steps was greater than 28%.

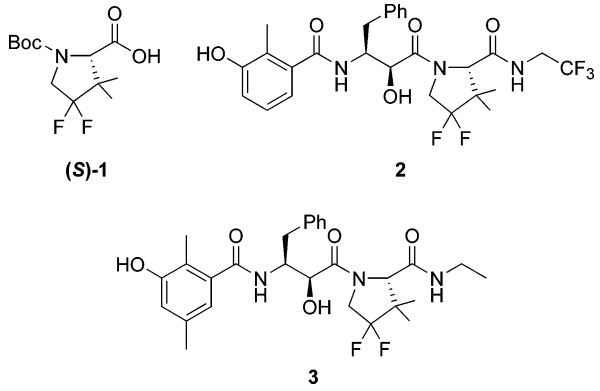
Introduction

Compound **(***S***)-1** is a key building block for a number of second-generation HIV protease inhibitors, such as **2** and **3**.[1] The original synthesis involved ketone fluorination with DAST or Deoxo-Fluor,[2] which are hazardous and expensive, and fluorination yields were less than 50%. To accommodate large-scale production, a fluorination-free synthesis was sought.

Results and Discussion

The synthetic strategy was to form pyrrolidinone **7** from acyclic amide **6** via iodolactamization (Scheme 1), followed by substitution, protecting group exchange, and oxidation-state adjustment to give **(**±**)-1**. A Claisen rearrangement was expected to establish the adjacent *gem* difluoro and dimethyl quaternary carbons of acid **5**.

Although formation of 2,2-difluoropent-4-enoic acid from allyl chlorodifluoroacetate via sequential Reformatskii and Claisen reactions is well studied and high yielding[3] (Scheme 2), a similar reaction sequence with acetate **4** under identical conditions resulted only in fragmentation to difluoroacetic acid and isoprene (Scheme 3). Experiments showed that ester **4** was unstable at high temperatures under acidic or basic conditions and liberated isoprene by 1,4-elimination. Traditional zinc activation techniques such as iodine or ethylene dibromide induction, or acid washing, failed to facilitate the conversion of **4** to **5**.



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(3) (a) Greuter, H.; Lang, R. W.; Romann, A. J. *Tetrahedron Lett.* **1988**, *29*, 3291. (b) Tang, W.; Borel, A. G.; Fujimiya, T. ; Abbott, F. S. *Chem. Res. Toxicol.* **1995**, *8*, 671.

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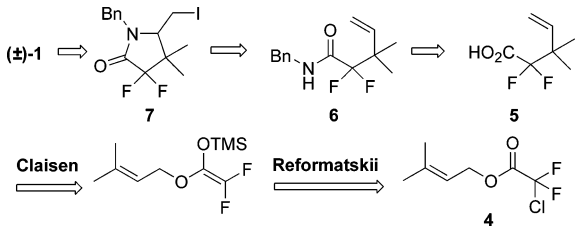
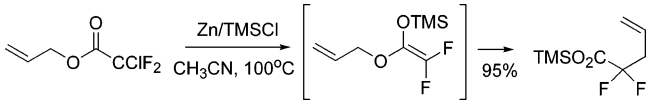
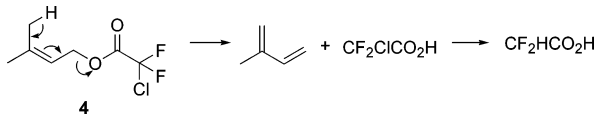
SCHEME 1



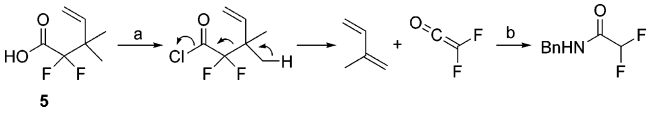
SCHEME 2



SCHEME 3

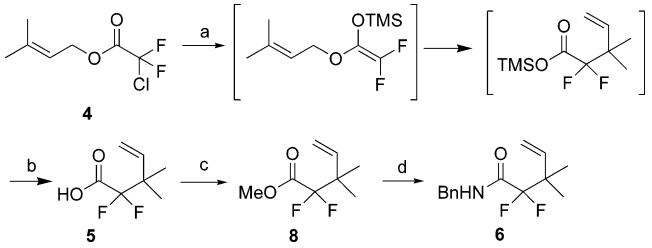


SCHEME 4 [a]



[a] Key: (a) $(COCl)_2$; (b) $BnNH_2$.

SCHEME 5 [a]



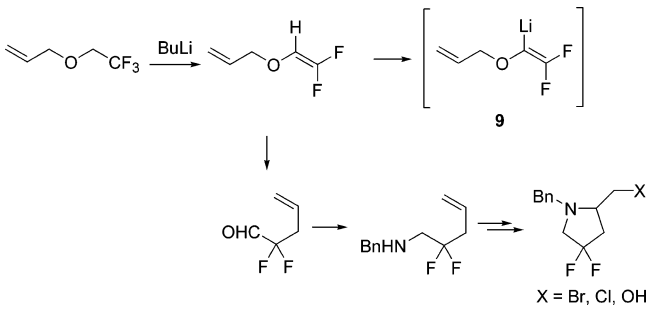
[a] Key: (a) (i) Zn, TMSCl, DMI, 25 °C, (ii) 100 °C; (b) H_2O, 68% from **4**; (c) H_2SO_4, $CH(OMe)_3$, 88%; (d) $BnNH_2$, DMAP, EtOAc, 96%.

Britton reported mild conditions to form 2,2-difluoroketene silyl acetals from chlorodifluoroacetates in 1,3-dimethylimidazolidin-2-one (DMI) solvent.[4] When these conditions were tested on substrate **4**, a >50% yield of crude **5** was obtained. Acid **5** was converted to the corresponding acid chloride and was then treated with benzylamine. A large amount of *N*-benzyldifluoroacetamide was obtained, which was likely due to formation of difluoroketene by fragmentation of the acid chloride (Scheme 4). To avoid ketene formation, acid **5** was first converted to methyl ester **8** using methyl orthoformate and sulfuric acid. Ester **8** was then reacted with benzylamine to give amide **6** (Scheme 5).

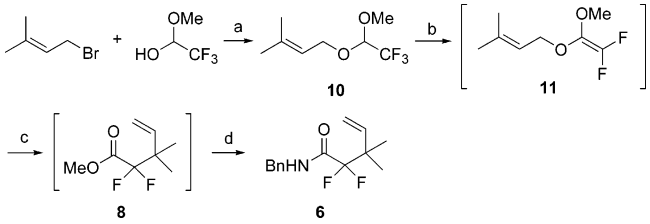
Although the Reformatskii−Claisen sequence produced desired acid **5**, the process generated a large amount of $ZnCl_2$ waste, offered relatively low yields, and was not ideal for large-scale production. Trifluoroethyl allyl ethers have been used widely as Claisen precursors by dehydrofluorination to produce 2,2-difluoropent-4-enal derivatives,[5] which in turn could be converted to pyrrolidine derivatives through a radical cyclization

(4) Britton, Thomas C. U.S. Patent 5,618,951, 1997.

SCHEME 6



SCHEME 7 [a]



[a] Key: (a) powdered K_2CO_3, *n*-Bu_4NBr, THF, 23 °C; (b) *n*-BuLi, THF, <−60 °C; (c) $BnNH_2$, <−60 °C; (d) warm to 0 °C, 80% from trifluoroacetaldehyde methyl hemiacetal.

or an epoxidation−cyclization sequence (Scheme 6). But under the strongly basic dehydrofluorination conditions, the newly formed difluorovinyl ether presumably underwent further deprotonation to generate highly reactive vinyllithium species **9**, which likely decomposed under the reaction conditions. To avoid vinyllithium formation, acetal **10**, whose corresponding vinyl ether has no acidic vinyl proton, was investigated (Scheme 7). Commercially available trifluoroacetaldehyde methyl hemiacetal was reacted with 3,3-dimethylallyl bromide to give acetal **10** in nearly quantitative yield. Compound **10** was treated with *n*-BuLi to generate vinyl ether **11**, which underwent a Claisen rearrangement upon warming to about 0 °C. Theoretically, only 1 equiv of *n*-BuLi was needed for this transformation, but in practice, 2 equiv of *n*-BuLi was required to complete the conversion to **8**. The need for an additional 1 equiv of *n*-BuLi was possibly due to formation of an insoluble *n*-BuLi·LiF complex. Benzylamine was then added to the basic mixture to form amide **6**, which was thus formed directly without isolation of ester **8**.

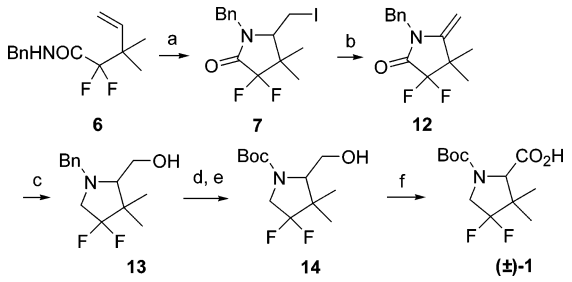
Since iodolactamization[6] does not usually give good results with secondary amides,[7] we were delighted to see high yields obtained with secondary amide **6** (Scheme 8).[8] Displacement of iodide from lactam **7** with oxygenated nucleophiles was unsuccessful. Even mild conditions by reaction with silver trifluoroacetate resulted predominantly in elimination product **12**. Given the difficulties with the substitution attempts, lactam **7** was treated with DBU to give a quantitative yield of enamide **12**. The latter was treated with in situ-formed borane, followed by H_2O_2, to achieve hydroboration and reduction in one pot to give alcohol **13**. A protecting group change converted **13** to the requisite Boc amino alcohol **14**. Finally, oxidation of alcohol **14** with $NaClO_2$, catalytic NaClO, and TEMPO gave carboxylic

(5) (a) Metcalf, B. W.; Jarvi, E. T.; Burkhart, J. P. *Tetrahedron Lett.* **1985**, *26*, 2861. (b) Garayt, M. R.; Percy, J. M. *Tetrahedron Lett.* **2001**, *42*, 6377.

(6) Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006.

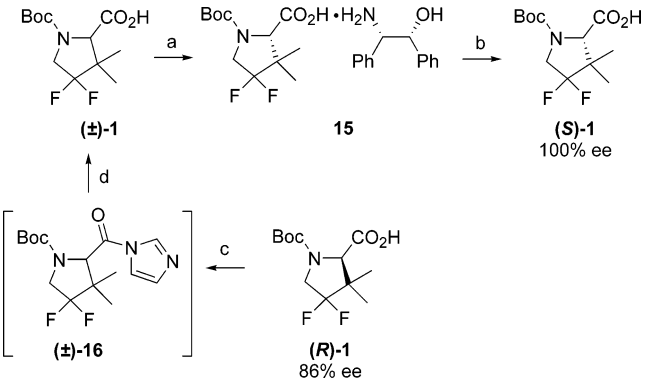
(7) Knapp, S.; Gibson, F. S.; Choe, Y. H. *Tetrahedron Lett.* **1990**, *31*, 5397.

SCHEME 8 [a]



[a] Key: (a) (i) TMSOTf, NEt_3, hexanes, (ii) I_2, CH_3CN, 90%; (b) DBU, EtOAc, reflux; (c) (i) $NaBH_4$, $BF_3{\cdot}Et_2O$, THF, (ii) 50% H_2O_2, 50% NaOH; (d) Pd/C, H_2, aq HCl, THF; (e) Boc_2O, 2 N NaOH; (f) $NaClO_2$, NaClO, TEMPO, 66% from **7**.

SCHEME 9 [a]



[a] Key: (a) (i) (1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol, CH_3CN/EtOH (9:1), (ii) CH_3CN/EtOH (9:1), 50 °C, 70%; (b) (i) 1 N HCl, EtOAc, (ii) crystallize from CH_3OH/H_2O, 86%; (c) (i) CDI, THF, (ii) DABCO, 50 °C; (d) NaOH (aq), 82%.

acid **(**±**)-1**. Because the late intermediates are either low melting solids or exhibit significant water solubility, no purification was conducted after compound **7**. A simple acid−base extractive workup was effective at removing virtually all impurities and yielded **(**±**)-1** in 66% yield from iodolactam **7**.

(*S***)-1** was prepared by a classical chemical resolution with (1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol in 30% chemical yield and 100% ee (Scheme 9). A procedure for recycling the undesired enantiomer was also established. (*R*)-Enriched **1** (86% ee), from the supernatant of **15**, was converted to the corresponding acyl imidazole **16**. Exposure of **16** to DABCO at 50 °C, followed by hydrolysis with aqueous NaOH, provided nearly racemic **1** (6% ee) suitable for reuse.

Conclusions

Difluorodimethylproline derivative **(***S***)-1** was prepared from commercially available trifluoroacetaldehyde methyl hemiacetal in 12 steps. Hazardous fluorination was avoided, and the overall yield was greater than 28%. A new synthesis of key intermediate amide **6** from trifluoroacetaldehyde methyl hemiacetal through an elimination−Claisen rearrangement sequence was developed.

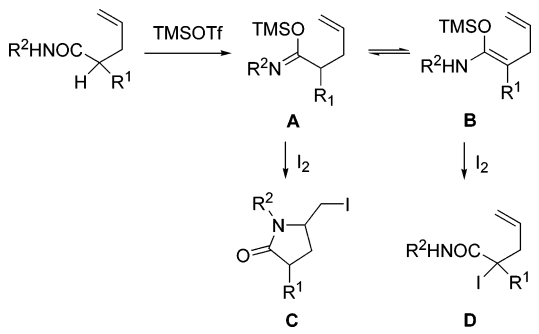
Experimental Section

General Experimental Information. ^1H NMR (300 MHz), ^{13}C NMR (75 MHz), and ^{19}F NMR (282 MHz) spectra were recorded with a 300 MHz NMR spectrometer. ^{19}F data are reported in ppm relative to C_6H_5F, and the ^{19}F spectra were ^1H-coupled unless otherwise specified. High-resolution mass spectral analyses were conducted using a mobile phase system of 1:1 H_2O/MeOH + 0.1% HCO_2H. GC−MS analyses were conducted with a 30.0 m × 250 μm × 0.25 μm column and a 50−250 °C temperature gradient. Achiral HPLC analyses were performed on a 3 μm ODS(3) 100A column (100 × 4.6 mm), 35 °C column chamber, 1.0 mL/min flow rate, 254 nm UV detection, and a linear gradient with 0.1% CF_3CO_2H /H_2O (solvent A) and 0.1% CF_3CO_2H/CH_3CN (solvent B) [gradient: 90% solvent A (0 min) → 35% solvent A (10 min) → 10% solvent A (12 min) → 10% solvent A (15 min)]. Chiral HPLC analyses were performed with a 4.6 × 150 mm column, 40 °C column chamber, 0.5 mL/min flow rate, 205 nm UV detection, an isocratic solvent system consisting of 0.1% CF_3CO_2H/H_2O (75%) and CH_3CN (25%), and a total run time of 25 min. TLC analyses were conducted with precoated silica gel plates [Si250F (250 μm)], which were visualized under UV light and then stained with a solution of phosphomolybdic acid/ethanol. Melting points were uncorrected.

Preparation of 3-Methylbut-2-enyl 2-Chloro-2,2-difluoroacetate (4). 3-Methylbut-2-en-1-ol (11.1 mL; 109 mmol) and NEt_3 (24.0 mL; 172 mmol) were dissolved in MTBE (80 mL). DMAP (0.2 g; 1.6 mmol) was added, and the solution was then cooled to −10 °C. Chlorodifluoroacetic anhydride (20.0 mL; 115 mmol) was added dropwise such that the internal temperature remained between −10 and 0 °C. After being stirred at −10 °C for 20 min, the solution was warmed to ambient temperature and stirred overnight. The solution was cooled to 0 °C and was then quenched with 20% aqueous citric acid (100 mL). The layers were separated, and the aqueous fraction was then extracted with MTBE (100 mL). The combined MTBE extracts were washed sequentially with 20% aqueous citric acid (100 mL), saturated aqueous NaCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and saturated aqueous NaCl (100 mL). After drying over Na_2SO_4, concentration in vacuo gave 22.1 g (100%) of **4** as a light-brown liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 5.38−5.46 (m, 1H), 4.85 (d, J = 7.4, 2H), 1.82 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5 (t, J = 34.0 Hz), 142.7, 117.4 (t, J = 300.7 Hz), 116.6, 65.3, 25.9, 18.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ 49.4 (s); IR (neat) 1775, 1298, 1165, 1119, 960, 900, 814, 728 cm^{-1}.

Preparation of 2,2-Difluoro-3,3-dimethylpent-4-enoic Acid (5). TMS-Cl (129 mL; 1.02 mol) was added to a suspension of Zn dust (66.9 g; 1.02 mol) and DMI (40 mL), and the mixture was then cooled to 15 °C. A solution of **4** (76.1 g of 89% purity; 341 mmol) and DMI (10 mL) was added such that the internal temperature remained between 15 and 20 °C. The mixture was stirred at 0 °C for 30 min and then at ambient temperature for 24 h, while being monitored by GC−MS. The mixture was heated at 100 °C for 7 h, while volatiles were removed. The mixture was cooled to room temperature and was then quenched with 5 N HCl (180 mL). After being stirred for 30 min, the mixture was filtered

(8) We believe that during silyl imidate formation there was an equilibrium between **A** and **B** when an α-proton was available. In some cases, we were able to isolate α-iodoamide **D** from the reaction mixture when an α-proton was present. Since no α-proton exists in amide **6**, only the pathway to **C** (and thus **7**) was possible.



and the solid was then washed with EtOAc (100 mL). The combined filtrate and wash were extracted with EtOAc (4 × 150 mL). The combined EtOAc extracts were washed with half-saturated aqueous NaCl (300 mL) and saturated aqueous NaCl (300 mL) and were then dried over Na_2SO_4. After concentration in vacuo, 75.8 g of crude **5** was obtained as a dark liquid. ^{1}H NMR indicated approximately 50% purity, which was appropriate for the next step. Corrected for purity, the yield was ~68%: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 5.91−6.00 (m, 1H), 5.23 (s, 1H), 5.18 (d, J = 6.8 Hz, 1H), 1.24 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (t, J = 33.6 Hz), 139.2 (t, J = 3.7 Hz), 118.1 (t, J = 257.2 Hz), 116.3, 43.4 (t, J = 21.4 Hz), 20.9 (t, J = 3.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −1.32 (s); IR (neat) 3094, 2989, 1747, 1470, 1419, 1388, 1277, 1229, 1183, 1112, 1067, 1036, 998, 926, 778, 709, 672 cm^{-1}.

Preparation of Methyl 2,2-Difluoro-3,3-dimethylpent-4-enoate (8). A mixture of crude **5** (47.2 g of ~61% purity; 175 mmol), $HC(OMe)_3$ (57.5 mL; 526 mmol), MeOH (57.5 mL), and H_2SO_4 (3.5 mL) was heated at 35 °C for 19 h. The mixture was cooled to 5 °C with an ice bath and was then quenched with saturated aqueous $NaHCO_3$ (300 mL). The mixture was extracted with EtOAc (150 mL), and the resulting aqueous fraction was then extracted with EtOAc (3 × 60 mL). The combined EtOAc extracts were washed with saturated aqueous $NaHCO_3$ (3 × 100 mL) and then with saturated aqueous NaCl (3 × 100 mL). After drying over Na_2SO_4 and concentration in vacuo, 32.6 g crude of **8** was obtained as a dark oil. ^{1}H NMR indicated approximately 85% purity, which was appropriate for the next step. Corrected for purity, the yield was ~88%: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (dd, J = 10.9, 17.3 Hz, 1H), 5.21 (d, J = 10.7 Hz, 1H), 5.17 (d, J = 17.6 Hz, 1H), 3.85 (s, 3H), 1.22 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6 (t, J = 33.4 Hz), 139.6 (t, J = 3.6 Hz), 118.3 (t, J = 257.5 Hz), 115.8, 53.2, 43.5 (t, J = 21.5 Hz), 21.0 (t, J = 3.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −0.85 (s); IR (neat) 1764, 1307, 1113, 1066, 1040, 926, 805, 738, 680 cm^{-1}.

Preparation of *N*-Benzyl-2,2-difluoro-3,3-dimethylpent-4-enamide (6) (Reformatskii−Claisen Procedure). Benzylamine (36.2 mL; 331 mmol) was added to a mixture of crude **8** (39.4 g of ~75% purity; 166 mmol). The resulting mixture was stirred overnight at ambient temperature for 23 h, while being monitored by GC. The mixture was adjusted to pH 2−3 with 1 N HCl (~300 mL required). The mixture was extracted with EtOAc (125 mL), and the resulting aqueous fraction was extracted with EtOAc (3 × 75 mL). The combined EtOAc extracts were washed sequentially with 1 N HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and saturated aqueous NaCl (100 mL). After drying over $MgSO_4$ and concentration in vacuo, 40.1 g of crude **6** was obtained as an oil. ^{1}H NMR indicated approximately 85% purity, which was appropriate for the next step. Corrected for purity, the yield was ~81%: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.11 (br s, 1H), 7.21−7.37 (m, 5H), 5.95 (dd, J = 10.7, 17.6 Hz, 1H), 5.16 (d, J = 5.7 Hz, 1H), 5.11 (s, 1H), 4.32 (d, J = 6.1 Hz, 2H), 1.14 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.1 (t, J = 29.6), 140.0 (t, J = 3.9 Hz), 138.9, 128.6, 127.7, 127.3, 119.1 (t, J = 257.7 Hz), 115.5, 43.1 (t, J = 21.9 Hz), 42.6, 21.1 (t, J = 3.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −1.25 (s); MS (CI) m/z 254.1342 (254.1356 calcd for $C_{14}H_{18}NOF_2$, M + H$^+$); IR (neat) 3324, 1698, 1681, 1541, 1130, 1097, 1080, 973, 923, 719, 695, 677 cm^{-1}.

Preparation of (±)-3-Methyl-1-(2,2,2-trifluoro-1-methoxyethoxy)but-2-ene (10). A mixture of trifluoroacetaldehyde methyl hemiacetal (35.0 g; 269 mmol), K_2CO_3 (93.0 g; 673 mmol), *n*-Bu_4NBr (4.3 g; 13.5 mmol), and THF (160 mL) was cooled to 0 °C. 1-Bromo-3-methylbut-2-ene (34.1 mL; 296 mmol) was added, and the mixture was then allowed to warm to ambient temperature and stir for 18 h, while being montiored by GC−MS. The mixture was filtered, and the solids were washed with THF (100 mL). The combined filtrate and wash were concentrated in a vacuum to give 51.2 g of a ~ 20:1 mixture of **10** and the bis-allyl acetal [3-methyl-1-(2,2,2-trifluoro-1-(3-methylbut-2-enyloxy)ethoxy)but-2-ene] as an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34−5.42 (m, 1H), 4.66 (q, J = 4.2 Hz, 1H), 4.25 (d, J = 7.1 Hz, 2H), 3.53 (s, 3H), 1.80 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 122.2 (q, J = 284.9 Hz), 119.5, 97.2 (q, J = 34.6 Hz), 65.2, 55.5, 26.1, 18.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ 33.0 (d, J = 4.2 Hz); IR (neat) 1282, 1174, 1156, 1113, 1079, 988, 715 cm^{-1}. Characteristic data for 3-methyl-1-(2,2,2-trifluoro-1-(3-methylbut-2-enyloxy)ethoxy)but-2-ene impurity: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34−5.41 (m, 2H), 4.75 (q, J = 4.3 Hz, 1H), 4.23 (d, J = 7.0 Hz, 4H), 1.80 (s, 6H), 1.72 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 122.4 (q, J = 284.8 Hz), 119.8, 95.6 (q, J = 34.5 Hz), 64.9, 26.1, 18.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ 33.0 (d, J = 4.3 Hz);

Preparation of *N*-Benzyl-2,2-difluoro-3,3-dimethylpent-4-enamide (6) (Elimination−Claisen Procedure). A solution of crude **10** (5.00 mL; ~25 mmol) and THF (20 mL) was cooled to −70 °C. *n*-BuLi (21.0 mL of a 2.5 M solution in hexane; 52.5 mmol) was added slowly, such that the internal temperature remained between −70 and −50 °C. The resulting mixture was stirred at −75 °C for 15 min. Benzylamine (5.50 mL; 50.0 mmol) was added slowly, such that the internal temperature remained between −70 and −55 °C. The reaction was then warmed to ambient temperature for 0.5 h, at which time GC−MS analysis showed complete Claisen rearragement and amidation. The mixture was cooled to 0 °C, and 1.7 N HCl (70 mL) was then added. The mixture was extracted with EtOAc (75 mL). The organic fraction was washed sequentially with 0.5 N HCl (75 mL), H_2O (75 mL), saturated aqueous $NaHCO_3$ (75 mL), and saturated aqueous NaCl (75 mL) and was then dried over Na_2SO_4. After concentration in vacuo, 4.95 g (80% over two steps) of **6** was obtained as a brown oil.

Preparation of (±)-1-Benzyl-3,3-difluoro-5-(iodomethyl)-4,4-dimethylpyrrolidin-2-one (7). TMS-OTf (4.80 mL; 26.6 mmol) was added dropwise to a −3 °C solution of **6** (5.00 g; 19.7 mmol), NEt_3 (4.10 mL; 29.6 mmol), and hexanes (40 mL), such that the internal temperature did not rise above 6 °C. The mixture was warmed to ambient temperature and was then stirred for 1 h. The suspension was filtered, and the solid was then washed with hexanes (10 mL). The combined filtrate and wash were concentrated in vacuo. The residue was dissolved in THF (10 mL) and was then cooled to 0 °C. I_2 (6.01 g; 23.7 mmol) was added, and after being stirred at 0 °C for 5 min, the mixture was stirred at ambient temperature for 1.5 h. The mixture was cooled to 0 °C and was quenched with a solution of $NaHSO_3$ (0.75 g) and H_2O (10 mL). After being stirred vigorously for 10 min, the mixture was extracted with EtOAc (50 mL). The organic fraction was washed with saturated aqueous $NaHCO_3$ (50 mL) and then with saturated aqueous NaCl (50 mL). After drying over Na_2SO_4 and concentration in vacuo, 12.5 g of crude **7** was obtained as an oil. Crude **7** was dissolved in 95% EtOH (20 mL), and H_2O (10 mL) was then added dropwise to the stirring solution. After the mixture was stirred for 10 min, additional H_2O (10 mL) was slowly added. The resulting slurry was cooled to −5 °C and, after stirring for 5 min, was filtered. The crystals were washed with 30% EtOH (20 mL), and were then dried under vacuum at 55 °C overnight to give 6.68 g (89.4%) of **7** as a brown solid: mp = 76−77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.42 (m, 5H), 5.11 (d, J = 14.8 Hz, 1H), 4.30 (dd, J = 2.5, 14.8 Hz, 1H), 3.39−3.45 (m, 1H), 3.16−3.28 (m, 1H), 1.28 (d, J = 2.0 Hz, 3H), 1.01 (d, J = 2.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5 (dd, J = 29.6, 32.0), 135.6, 130.2, 129.8, 129.6, 119.4 (dd, J = 252.1, 257.7), 65.1 (J = 3.9 Hz), 46.7, 43.9 (t, J = 19.4), 23.3 (dd, J = 3.1, 7.6 Hz), 16.7 (d, J = 7.7 Hz), 0.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ 1.91 (d, J = 265.6 Hz), −12.4 (app dt, J = 265.7, 2.5 Hz); MS (CI) m/z 380.0339 (380.0323 calcd for $C_{14}H_{17}NOF_2I$, M + H$^+$); IR (neat) 1715, 1450, 1330, 1269, 1169, 1083, 1031, 979, 746, 693 cm^{-1}.

Preparation of 1-Benzyl-3,3-difluoro-4,4-dimethyl-5-methylenepyrrolidin-2-one (12). DBU (5.90 mL; 39.3 mmol) was added to a solution of **7** (7.46 g; 19.7 mmol) and EtOAc (15 mL) at ambient temperature. The mixture was heated at reflux for 1.5 h, while being monitored by HPLC. The mixture was cooled to room

temperature and quenched with 2 N HCl (20 mL). The mixture was then extracted with EtOAc (50 mL). The EtOAc extract was washed sequentially with 0.5 N HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and saturated aqueous NaCl (50 mL). After drying over Na_2SO_4 and concentration in vacuo, 4.97 g (100%) of crude **12** was obtained as an oil and used as is in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.39 (m, 5H), 4.77 (s, 2H), 4.43−4.45 (m, 1H), 4.36 (d, J = 3.0 Hz, 1H), 1.30 (t, J = 1.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1 (t, J = 31.2 Hz), 150.1 (t, J = 3.5 Hz), 135.0, 129.2, 128.3, 127.5, 117.9 (t, J = 255.0 Hz), 88.5, 44.6, 43.1 (t, J = 20.5 Hz), 21.1 (t, J = 5.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −7.04 (s); MS (CI) m/z 252.1204 (252.1200 calcd for $C_{14}H_{16}NOF_2$, M+H$^+$); IR (neat) 1744, 1655, 1390, 1288, 1156, 1091, 1065, 835, 754, 696 cm^{-1}.

Preparation of (±)-(1-Benzyl-4,4-difluoro-3,3-dimethylpyrrolidin-2-yl)methanol (13). $NaBH_4$ (1.68 g; 44.3 mmol) was added to a solution of **12** (4.96 g; 19.7 mmol) and THF (40 mL) at ambient temperature. The mixture was cooled to −4 °C, and BF_3·OEt_2 (10.0 mL) was then added such that the internal temperature remained < 0 °C. The resulting mixture was stirred at −10 to 0 °C for 2.5 h, while being monitored by HPLC. MeOH (5 mL) was added such that the internal temperature remained <5 °C. 50% H_2O_2 (10 mL) was then added such that the internal temperature remained <0 °C. After an additional 5 min, 50% NaOH (12 mL) was added (pH > 12). The suspension was stirred for 10 min and was then extracted with EtOAc (50 mL). The EtOAc extract was washed with H_2O (50 mL) and then with saturated aqueous NaCl (50 mL). After drying over Na_2SO_4 and concentration in vacuo, 4.58 g (91%) of crude **13** was obtained as an oil and was used as is in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.40 (m, 5H), 4.11 (d, J = 13.3 Hz, 1H), 3.77−3.82 (m, 1H), 3.63−3.68 (m, 1H), 3.51 (d, J = 13.3 Hz, 1H), 3.31 (ddd, J = 8.7, 11.9, 20.8 Hz, 1H), 2.88 (ddd, J = 8.6, 11.8, 19.6 Hz, 1H), 2.57 (br s, 1H), 1.15 (d, J = 2.3 Hz, 3H), 1.12 (d, J = 2.3 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 140.6, 130.4 (dd, J = 249.5, 257.1 Hz), 130.1, 129.8, 128.6, 73.9 (d, J = 3.9 Hz), 63.4, 60.9, 59.8 (t, J = 28.2 Hz), 46.6 (t, J = 20.0 Hz), 20.7 (d, J = 8.5 Hz), 17.8 (dd, J = 2.8, 7.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ 4.62 (dt, J = 227.1, 20.7 Hz), −2.57 (d, J = 226.6 Hz); MS (CI) m/z 256.1500 (256.1513 calcd for $C_{14}H_{19}NOF_2$, M + H$^+$); IR (neat) 3419, 2937, 1453, 1192, 1071, 1027, 900, 735, 698 cm^{-1}.

Preparation of (±)-*tert*-Butyl 4,4-Difluoro-2-(hydroxymethyl)-3,3-dimethylpyrrolidine-1-carboxylate (14). A suspension of crude **13** (4.58 g; 17.9 mmol) and 0.6 N HCl (50 mL) was stirred at 50 °C for 5 min. Activated charcoal (3 g) was added, and the mixture was then stirred at 50 °C for 5 min. The mixture was filtered through Celite, and the filter was then washed with H_2O (10 mL) and THF (30 mL). Pd/C (10%, 0.5 g wet) was added to the combined filtrate and wash, and the resulting mixture was hydrogenated with a Parr shaker (50 psi H_2). After hydrogenating overnight and monitoring by TLC (silica gel; 1:4 EtOAc/hexanes), the mixture was then filtered on Celite. The THF was removed by concentration in a vacuum (∼30 mmHg), and the resulting aqueous mixture was adjusted to ∼pH 10 with 2 N NaOH. Boc_2O (4.90 mL; 21.5 mmol) was added, and the mixture was then stirred at ambient temperature for 5 h while being monitored by TLC (silica gel; 1:4 EtOAc/hexanes). Glycine (1.34 g; 17.8 mmol) was added, and after being stirred at ambient temperature overnight, the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (100 mL) and then with saturated aqueous NaCl (50 mL). After drying over Na_2SO_4 and concentration in a vacuum, 4.70 g (99%) of crude **14** was obtained as an oil and was used as is in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.91 (br s, 1H), 3.58−3.77 (m, 5H), 1.48 (s, 9H), 1.16 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 126.9 (t, J = 251.9), 82.0, 68.9, 63.7, 52.5 (t, J = 31.9 Hz), 44.9 (t, J = 20.3 Hz), 28.7, 19.8 (d, J = 6.3 Hz), 16.6 (d, J = 3.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ 0.03 (dt, J = 232.0, 17.3 Hz), 4.50 (app dt, J = 231.7, 8.2 Hz); MS (CI) m/z 266.1591 (266.1568 calcd for $C_{12}H_{22}NO_3F_2$, M + H$^+$); IR (neat) 3425, 2978, 2897, 1677, 1473, 1393, 1368, 1353, 1250, 1164, 1131, 1105, 1090, 1045, 1010, 908, 895, 857, 774, 715, 703 cm^{-1}.

Preparation of (±)-1-(*tert*-Butoxycarbonyl)-4,4-difluoro-3,3-dimethylpyrrolidine-2-carboxylic Acid [(±)-1]. TEMPO (0.07 g; 0.44 mmol), KH_2PO_4 (1.21 g; 8.89 mmol), and a solution of $NaClO_2$ (3.00 g of ∼80% purity; 26.5 mmol) and H_2O (5 mL) were sequentially added to a solution of crude **14** (4.70 g; 17.7 mmol) and CH_3CN (5 mL) at ambient temperature. The mixture was cooled to 0 °C and stirred for 5 min. An aqueous solution of NaClO (1.0 mL of a 6.15% aqueous solution; 0.83 mmol) was added. The resulting dark purple mixture was stirred at 0 °C for 3 h while monitoring by TLC (silica gel; 1:4 EtOAc/hexanes). The reaction was quenched with 2% aqueous $NaHSO_3$ (25 mL) and was adjusted to pH 10 with 2 N NaOH. The mixture was washed with EtOAc (30 mL). The resulting aqueous fraction was filtered on Celite, and the filtrate was stirred under house vacuum (∼30 mmHg) for 2 h to remove volatiles and then adjusted to pH 3 with 1 N HCl to form a white suspension. After filtration, H_2O washing, and drying under vacuum at 55 °C overnight, 3.64 g (66% over four steps from **7**) of **1** was obtained as a white solid. The spectroscopic data was identical to that for **(*S*)-1**.

Preparation of (2*S*,3*R*)-2,3-Diphenyl-3-hydroxyethylammonium (*S*)-1-(*tert*-Butoxycarbonyl)-4,4-difluoro-3,3-dimethylpyrrolidine-2-carboxylate (15). (1*R*,2*S*)-(−)-2-Amino-1,2-diphenylethanol (3.82 g; 17.9 mmol) was added to a solution of **(±)-1** (10.0 g; 35.8 mmol), CH_3CN (90 mL), and absolute EtOH (10 mL) at ambient temperature. The resulting slurry was stirred at ambient temperature for 24 h. The suspension was filtered, and the white solid was washed with CH_3CN (50 mL) and was then dried under vacuum at 55 °C overnight to give 7.71 g of **15** with 53.0% de by chiral HPLC. This material was suspended in 9:1 CH_3CN/EtOH (77 mL) and was then heated at 50 °C for 24 h. After cooling to ambient temperature, the suspension was filtered and the solid was dried under vacuum at 55 °C overnight to give 6.20 g (35.1%) of **15** as a white solid: mp = 179−180 °C; chiral HPLC 96.6% de; ^{1}H NMR (300 MHz, CD_3OD) δ 7.19−7.35 (m, 8H), 7.08−7.15 (m, 2H), 5.20 (d, J = 4.2 Hz, 1H), 4.45 (d, J = 4.2 Hz, 1H), 3.93−3.99 (m, 1H), 3.72−3.90 (m, 2H), 1.45−1.48 (m, 9H), 1.26 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) major rotamer δ 172.7, 154.1, 142.0, 137.1, 130.9 (one central peak of CF_2 AB q), 129.1, 127.8, 127.7, 127.6, 127.1, 126.7, 124.2 (one central peak of CF_2 AB q), 79.4, 73.6, 69.6, 60.5, 51.3 (t, J = 31.6 Hz), 41.2 (t, J = 20.5 Hz), 28.3, 21.6−21.8 (m), 18.5−18.7 (m), minor rotamer δ 172.3, 153.7, 69.3, 51.9 (t, J = 31.7 Hz), 44.5 (t, J = 20.3 Hz), 28.4, 21.8−22.1 (m), 18.3−18.5 (m); ^{19}F NMR (282 MHz, CD_3OD, ^{1}H-decoupled) major rotamer δ −0.56 (AB q, J = 229.1 Hz, $\Delta\nu$ = 1099.0 Hz); minor rotamer δ 0.31 (AB q, J = 229.2 Hz, $\Delta\nu$ = 510.4 Hz); IR (neat) 3337, 2978, 1683, 1587, 1505, 1416, 1380, 1368, 1307, 1151, 1129, 1093, 1048, 911, 901, 769, 751, 718, 703 cm^{-1}.

Preparation of (*S*)-1-(*tert*-Butoxycarbonyl)-4,4-difluoro-3,3-dimethylpyrrolidine-2-carboxylic Acid [(*S*)-1]. Compound **15** (4.00 g; 8.12 mmol) was partitioned between EtOAc (90 mL) and 1 N HCl (90 mL) while being warmed to 30 °C to complete dissolution of **15**, and the resulting layers were separated. The EtOAc fraction was sequentially washed with H_2O (2 × 50 mL) and saturated aqueous NaCl (50 mL) and was then dried over $MgSO_4$, filtered, and concentrated to give 2.20 g (96.9%) of crude (*S*)-**1**. Crude **(*S*)-1** was dissolved in CH_3OH (6.6 mL) at ambient temperature, and H_2O (11.2 mL) was then slowly added to effect crystallization. The resulting crystal slurry was stirred at ambient temperature overnight. The suspension was filtered, and the solid was washed with H_2O (10 mL) and was then dried under vacuum at 50 °C overnight to give 1.95 g (85.9%) of **(*S*)-1** as white crystals: mp = 143−144 °C; chiral HPLC 100% ee; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.90 (br s, 1H), 3.95 (s, 1H), 3.74−3.87 (m, 2H), 1.41 (s, 3H), 1.36 (s, 6H), 1.22 (app d, J = 1.6 Hz, 3H), 1.04 (app d, J = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) major

rotamer δ 170.8, 153.3, 126.8 (dd, J = 251.2, 253.9 Hz), 80.3, 67.8, 51.0 (t, J = 31.5 Hz), 45.6 (t, J = 21.2 Hz), 28.1, 21.4 (app dd, J = 1.9, 6.6 Hz), 17.9 (app dd, J = 1.4, 6.5 Hz), minor rotamer δ 170.3, 153.7, 127.3 (dd, J = 252.2, 253.8 Hz), 80.8, 67.3, 51.5 (t, J = 31.9 Hz), 44.9 (t, J = 21.1 Hz), 28.3, 21.6 (app dd, J = 1.5, 7.1 Hz), 17.7 (d, J = 6.1 Hz); ^{19}F NMR (282 MHz, DMSO-d_6, ^{1}H decoupled) major rotamer δ 0.32 (AB q, J = 227.4 Hz, $\Delta\nu$ = 354.4 Hz), minor rotamer δ 1.10 (AB q, J = 227.1 Hz, $\Delta\nu$ = 578.0 Hz); MS (CI) m/z 280.1374 (280.1360 calcd for $C_{12}H_{20}NO_4F_2$, M + H^+); IR (neat) 2983, 1750, 1735, 1645, 1472, 1424, 1369, 1202, 1157, 1094, 908, 858, 765, 705 cm^{-1}.

Preparation of (±)-1-(*tert*-Butoxycarbonyl)-4,4-difluoro-3,3-dimethylpyrrolidine-2-carboxylic Acid [(±)-1] by Racemization of an (*R*)-Enriched Mixture. (*R*)-Enriched 1-(*tert*-butoxycarbonyl)-4,4-difluoro-3,3-dimethylpyrrolidine-2-carboxylic acid **1** (2.00 g; 7.16 mmol; 86% ee) was dissolved in anhydrous THF (20 mL) at ambient temperature. CDI (1.28 g; 7.88 mmol) was added, and the solution was stirred at ambient temperature, while being monitored by HPLC. Once conversion to the acyl imidazole was complete (~1 h), DABCO (0.803 g; 7.16 mmol) was added, and the solution was then heated to 50 °C. After the mixture was stirred for 2 days at 50 °C, chiral HPLC revealed a 47:53 ratio of *S*/*R* enantiomers. Aqueous NaOH (8.0 mL of a 1.5 M solution) was added, and the hydrolysis was monitored by HPLC. After hydrolysis was complete, the reaction mixture was diluted with MTBE (20 mL) and H_2O (20 mL). The biphasic mixture was acidified to ~pH 1 with concd HCl, and the layers were separated. The organic phase was washed with H_2O (10 mL) and then with saturated aqueous NaCl (10 mL). After drying over $MgSO_4$, filtration, and concentration, 1.64 g (82%) of 1-(*tert*-butoxycarbonyl)-4,4-difluoro-3,3-dimethylpyrrolidine-2-carboxylic acid was obtained as a white solid. Chiral HPLC revealed a 47:53 ratio of *S*/*R* enantiomers. The spectroscopic data was identical to that for **(*S*)-1**.

Supporting Information Available: NMR spectra for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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