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Synthesis of a complete series of C-4 fluorinated Phe-Gly mimetics

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Abstract

The complete series of Boc-protected allylic mono- and difluorinated Phe-Gly methyl ester derivatives has been synthesized using facile methods. Diastereomeric allylic alcohol derivatives were used as key intermediates. *cis*- And *trans*-aziridine derivatives were synthesized in high yields from the diastereomeric alcohols using Mitsunobu conditions. The aziridines were treated with diethylaminosulfur trifluoride (DAST) at room temperature, which resulted in stereoselective ring openings yielding the monofluorinated derivatives. The difluorinated isostere was synthesized from the γ-keto ester derivative using DAST. Also the corresponding series of saturated fluorinated derivatives was synthesized.

Keywords: Aziridines; Fluorine and compounds; Halogenation; Peptide mimetics

The similarity in size but substantial difference in electrostatic properties between fluorine and hydrogen makes fluorination an interesting strategy in the design of biologically active compounds.[1,2] In the field of dipeptidomimetics containing amide bond isosteres,[3] comparisons of a vinyl isostere[4] with a fluorovinyl group[5,6] demonstrated that the fluorine containing amide isosteres can exhibit excellent mimicking abilities. In the present study we report the facile syntheses of a complete series of novel mono- and difluoroallyl Phe-Gly dipeptidomimetics and their corresponding saturated derivatives. These compounds may act as a complement to the previously reported fluorovinyl isosteres. Their different fluoro substitutions should, according to electrostatic potential maps, give as interesting peptide mimicking properties as the fluorovinyl isosteres.

RESULTS AND DISCUSSION

Several different reagents for fluorination of alcohols have been suggested,[7] *e.g.* the frequently used diethylaminosulfur trifluoride (DAST).[8] DAST can be used in the synthesis of mono-fluorinated derivatives from the corresponding alcohols[9] and in the synthesis of difluorinated derivatives from the corresponding ketones.[10] We therefore planned to use the unsaturated ketone isostere **5** as a starting material for both the mono- and the difluorinated derivatives. Scheme 1 shows the synthetic pathway leading to **5**.

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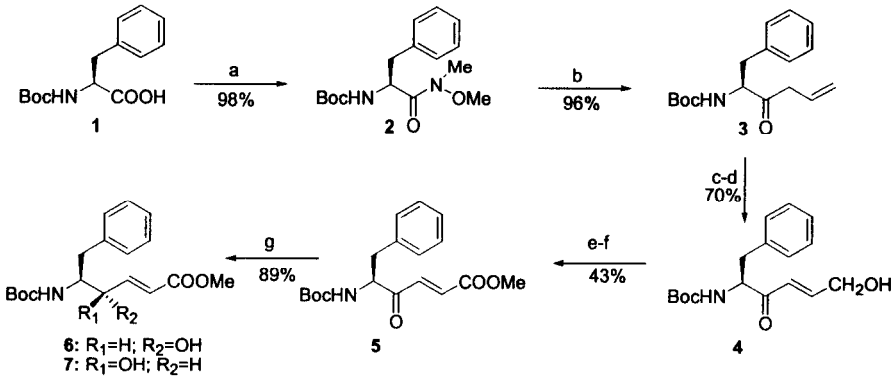
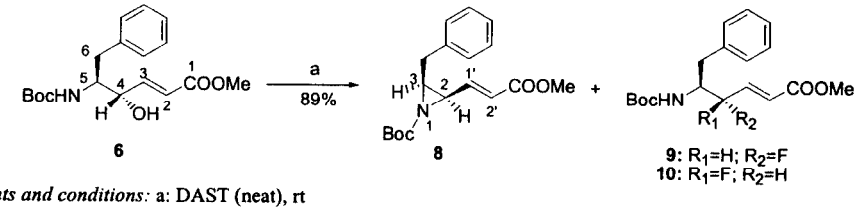
Scheme 1.



Reagents and conditions: a: *N*-methoxy-*N*-methylamine hydrochloride, Et_3N, 2-chloro-1-methylpyridinium iodide, CH_2Cl_2, reflux; b: allyl magnesium bromide, THF, -40 °C; c: *m*-CPBA, CH_2Cl_2, rt; d: silica gel; e: MnO_2, hexane/CH_2Cl_2, 0 °C; f: PDC, DMF, MeOH, rt; g: $NaBH_4$, $CeCl_3$, THF-MeOH, rt.

The synthesis of ketone **3** from *tert*-butoxycarbonyl (Boc) protected L-phenylalanine (**1**) *via* the Weinreb amide **2** was performed according to Kim *et al.*[11] Epoxidation of **3** using 3-chloroperbenzoic acid (*m*-CPBA) needed careful monitoring since we could observe some isomerization of the double bond into conjugation with the carbonyl group if the reaction time was prolonged.[12] When the epoxide was purified by flash chromatography it was found to be unstable: Contact with silica resulted in an epoxide ring opening providing the desired allylic alcohol **4**.[13] Therefore, the crude reaction mixture from the epoxidation was passed through a silica gel column to provide the allylic alcohol **4** in 70% yield (calculated from **3**). Alcohol **4** was oxidized to the methyl ester **5** in two steps: The first step was an oxidation to the aldehyde using activated MnO_2,[14] followed by a PDC-oxidation in a mixture of methanol and DMF[15] to produce the methyl ester **5**. The keto function of **5** was selectively reduced using $NaBH_4$ in the presence of $CeCl_3$[16] affording a 1:1 mixture of alcohol isomers **6** and **7**. Pure **6** and **7** were obtained after separation by column chromatography and recrystallization. The diastereomeric purity of **6** conformed with that obtained when **6** was synthesized *via* a different route.[17] Thus, the synthetic procedure to alcohols **6** and **7** shown in Scheme 1 did not result in epimerization at C-5.

Scheme 2.



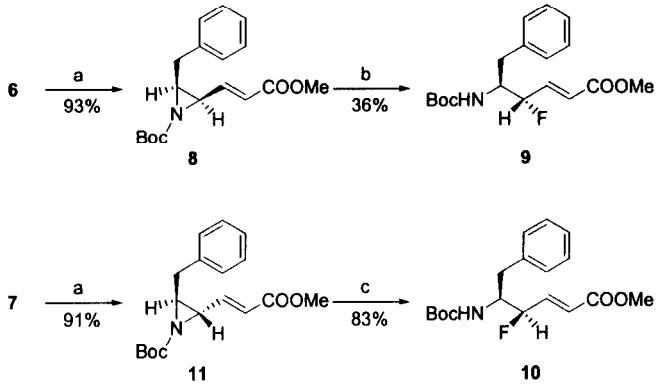
Reagents and conditions: a: DAST (neat), rt

In an initial attempt to synthesize the fluoroallyl derivatives, alcohol **6** was reacted with DAST at room temperature (Scheme 2). However, the reaction produced the *cis*-aziridine **8** as the major product together with an epimeric mixture of fluorinated derivatives **9** and **10**, compound **9** being the major isomer (Scheme 2).[18] When the reaction was repeated at -78 °C only **8** was isolated. This suggests that the synthesis of **9** from **6**

(Scheme 2), which proceeds with retention of the configuration at C-4, could involve aziridine **8**, which has an inverted configuration at C-4, as an intermediate.

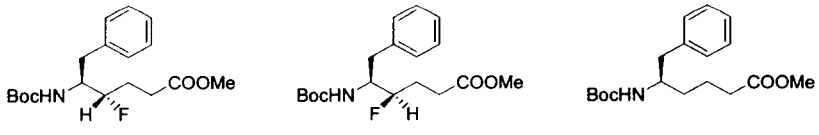
To investigate this reaction mechanism we synthesized both the *cis*- and *trans*-aziridines (**8** and **11**, respectively). The aziridines were obtained from the epimeric alcohols **6** and **7** in 93 and 91% yield, respectively, using Mitsunobu conditions (Scheme 3).[19] These reaction conditions gave higher yields than the alternative aziridine formation using DAST.

Scheme 3.



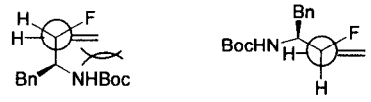
Reagents and conditions: a: PPh_3, DEAD, THF, reflux; b: DAST (neat), $SbCl_3$, rt; c: DAST, CH_2Cl_2, molecular sieves, rt.

In separate experiments, the *cis*- and *trans*-aziridines were then reacted with DAST to afford **9** in 36% yield[20] and **10** in 83% yield,[21] respectively (Scheme 3). This is consistent with the hypothesis of an involvement of an aziridine as an intermediate in the formation of fluorinated derivatives from alcohols with DAST. Most likely, the observed formation of the minor epimer **10** from **6** was due to an S_N2-reaction (Scheme 2).[22] The aziridines showed considerable differences in reactivities in the reaction with DAST, the *trans* isomer being more reactive. Thus, the *cis*-aziridine is formed more readily than the *trans*-aziridine and the *trans*-aziridine is more reactive in nucleophilic ring opening reactions than the *cis*-aziridine.



The saturated fluorinated derivative **12** was obtained in high yield by hydrogenation of **9** using Pd/C. Interestingly, in the reduction of **10** with Pd/C, compound **13** and the defluorinated derivative **14** were formed in equal amounts.[23] The use of PtO_2 as the catalyst in the hydrogenation reaction only resulted in an increased formation of **14**. It has been shown that metal catalyzed hydrogenations of allylic fluorides can result in dehalogenation and a concomitant saturation of the double bond.[23] In our case, the difference in results from hydrogenation reactions of the isomeric fluoroallyl derivatives **9** and **10** was unexpected. However, inspection of

molecular models indicate that the proposed transition state for defluorination is more crowded in reactions of **9** compared to that in **10** (Figure 1).



9 **10**

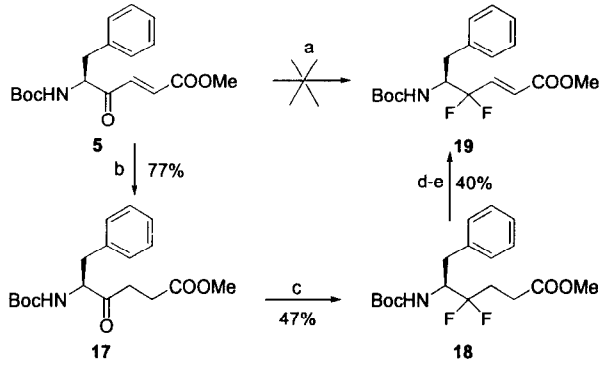
Figure 1. Relevant conformations for the palladium catalyzed defluorinations of **9** (left) and **10** (right). The fluorine atom and the double bond are expected to be periplanar in the transition state of the reaction.

Also the unsaturated alcohols **6** and **7** were hydrogenated in high yields: Reduction of **6** gave the expected saturated alcohol **15** in 89% yield, whereas reduction of **7** produced lactone **16** as the only product (99% yield). Most likely, the increased conformational freedom of the reduced structure made an intramolecular cyclization possible, thus producing the thermodynamically stable lactone **16**. Although the saturated alcohol **15** also has an increased conformational freedom, steric interactions appear to prevent an intramolecular cyclization. Molecular

15 **16**

mechanics calculations of the two isomeric lactones indicate that the lactone formed from **6** is more sterically crowded. The difference in steric energy between the two isomers is 6.8 kJ/mol. The steric energies of the two alcohols only differ by 0.6 kJ/mol. Thus, assuming a product-like transition state, it appears that a significant difference in activation energy determines the different abilities of the saturated alcohols to form lactones.

Scheme 4.



Reagents and conditions: a: DAST (neat), 50-60 °C, 10 days; b: H_2, Pd(C), pyridine, rt; c: DAST, (neat), 50-60 °C; d: i) LDA, ii) PhSeBr, THF; e: *m*-CPBA, CH_2Cl_2, rt.

Geminal difluorinated compounds can be obtained from the corresponding ketones.[10] However, reaction of ketone **5** with DAST afforded only minute amounts of product even after prolonged heating (Scheme 4). We

believe that the low reactivity is due to the stability of the conjugated system that decreases the Lewis basicity of the carbonyl oxygen. Therefore, we used the saturated derivative **17** as starting material for the difluorination. Selective hydrogenation of the double bond in **5** using Pd/C in pyridine afforded **17** in 77% yield (Scheme 4).[24] Compound **17** could thereafter be converted to the difluorinated derivative **18** in 47% yield by treatment with DAST. To obtain the unsaturated difluorinated derivative **19** the double bond was reintroduced into **18**; reaction of the enolate of **18** with phenylselenium bromide followed by oxidation/elimination using *m*-CPBA afforded **19**[25] in an overall yield of 40% (Scheme 4). Only the *E*-isomer of the alkene was formed.

CONCLUSION

We have synthesized a series of unsaturated and saturated mono- and difluorinated Phe-Gly mimetics in a stereoselective and controlled fashion. The mimicking ability of the synthesized mimetics will be evaluated after replacement of Phe-Gly dipeptidic moieties in biologically active peptides, such as substance P and dermorphin. Both these peptides contain Phe-Gly fragments in domains considered important for receptor binding and activation.[26]

EXPERIMENTAL

General.[17,27] The ^{19}F NMR spectra were obtained on a JEOL JNM-EX400 spectrometer with CCl_2F_2 as internal standard. The numbering of the atoms is given in Scheme 2. In analytical HPLC a LiChroCART 4 × 250 mm, 5-μm LiChrospher Si 60 column was used. Infrared spectra were recorded on a Perkin-Elmer 1605 FT-IR spectrophotometer. The syntheses of **2**,[11] **3**[11] and **6**[17,28] have been described elsewhere.

(*S*)-5-[(*tert*-Butoxycarbonyl)amino]-1-hydroxy-6-phenyl-(*E*)-2-hexen-4-one (4). *m*-CPBA (660 mg, 3.8 mmol) was added to a solution of **3** (500 mg, 1.7 mmol) in CH_2Cl_2 (50 mL). After stirring at room temperature for 66 h the reaction mixture was washed with saturated aqueous $NaHCO_3$ and brine. The organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (*n*-pentane:ether 3:1) gave **4** (372 mg, 70%) as a colorless oil: HPLC (4% EtOH in *n*-hexane), 1.5 mL/min, t_R 11.9 min; $[\alpha]_D$ = +48.4 (*c* 3.83, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.28-7.12 (m, 5H, Ph), 7.00 (dt, 1H, *J* = 15.5, 4.1 Hz, H-2), 6.48 (d, 1H, *J* = 15.5 Hz, H-3), 5.26 (d, 1H, *J* = 7.0 Hz, NH), 4.79 (app q, 1H, *J* = 7.0 Hz, H-5), 4.33 (app s, 2H, H-1), 3.13 (dd, 1H, *J* = 14.0, 6.6 Hz, H-6a), 2.99 (dd, 1H, *J* = 14.0, 5.8 Hz, H-6b), 2.13 (br s, 1H, OH), 1.41 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 197.17 (C-4), 155.18 (*Boc* C=O), 147.30 (C-2), 135.98 (C-1'), 129.47 (2 C:s), 128.41 (2 C:s) (C-2', C-3'), 126.85 (C-4'), 124.70 (C-3), 79.82 [$(CH_3)_3C$], 61.88 (C-1), 58.79 (C-5), 37.96 (C-6), 28.26 (3 C:s) [$(CH_3)_3C$]; IR (KBr) 3424, 1696 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.68; H, 7.48; N, 4.55.

Methyl (5*S*)-5-[(*tert*-butoxycarbonyl)amino]-4-oxo-6-phenyl-(*E*)-2-hexenoate (5). Compound **4** (394 mg, 1.25 mmol) was dissolved in a 1:5 mixture of hexane and CH_2Cl_2 (64 mL). Activated manganese dioxide (3.8 g, 43.9 mmol) was added. After stirring under N_2 atmosphere at 0° C for 0.5 h, the reaction was quenched by filtration through a celite pad washed with ether (3 × 10 mL). The solvent was removed in vacuo to afford crude aldehyde as a light yellow oil, which was used in the next step without further purification.

Pyridinium dichromate (2.8 g, 7.5 mmol) was added to a solution of the crude aldehyde in MeOH (0.5 mL) and dry DMF (14 mL) at room temperature under N_2 atmosphere. The reaction mixture was stirred at room temperature for 18 h. The solution was poured into a mixture of hexane (60 mL) and water (20 mL). The mixture was filtered through a celite pad. The water layer was extracted with hexane (3 × 20 mL) and the combined hexane extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (*n*-hexane/ether 3:1) and recrystallization (*n*-hexane) gave **5** (180 mg, 43%) as white needles: HPLC (1% EtOH in *n*-hexane), 1.5 mL/min, t_R 7.0 min; mp 92-94 °C; $[\alpha]_D$ = +7.3 (*c* 0.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.31-7.09 (m, 6H, Ph, H-2), 6.77 (d, 1H, *J* = 15.8 Hz, H-3), 5.14 (d, 1H, *J* = 7.3 Hz, NH), 4.78 (app q, 1H, *J* = 6.3 Hz, H-5), 3.81 (s, 3H, OCH_3), 3.17 (dd, 1H, *J* = 13.8, 6.3 Hz, H-6a), 3.00 (dd, 1H, *J* = 13.8, 6.3 Hz, H-6b), 1.41 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 197.18 (C-4), 165.52 (C-1), 155.04 (*Boc* C=O), 136.35 (C-1'), 135.40 (C-2), 131.70 (C-3), 129.29 (2 C:s), 128.61 (2 C:s) (C-2', C-3'), 127.08 (C-4'), 80.13 [$(CH_3)_3C$], 59.70 (C-5), 52.36 (OCH_3), 37.16 (C-6), 28.18 (3 C:s) [$(CH_3)_3C$]; IR (KBr) 1723, 1686 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_5$ × 0.25 H_2O: C, 64.40; H, 7.01; N, 4.14. Found: C, 64.16; H, 6.97; N, 4.11.

Methyl (4*S*,5*S*)-5-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-6-phenyl-(*E*)-2-hexenoate (6) and Methyl (4*R*,5*S*)-5-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-6-phenyl-(*E*)-2-hexenoate (7). Compound **5** (4 g, 12 mmol) and $CeCl_3$ × 7 H_2O (4.5 g, 12 mmol) were dissolved in THF/MeOH (2:1) (210 mL). $NaBH_4$ (0.9 g, 24 mmol) was added slowly while stirring. After 10 min at room temperature the reaction was quenched by addition of H_2O and $CHCl_3$. The organic phase was washed with H_2O and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by flash chromatography (*n*-hexane:ether 1:1) yielding a 1:1 mixture of **6** and **7**. Flash chromatography (*n*-hexane:ether 1:1) and recrystallization from $CHCl_3$/*n*-hexane gave pure **6** and **7** in a total yield of 89%. For data on **6** see reference 17.

7: HPLC (2.0% EtOH in *n*-hexane), 1.5 mL/min, t_R 15.9 min; mp 147-148 °C; $[\alpha]_D$ = -7.4 (*c* 0.68, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.33-7.17 (m, 5H, Ph), 7.00 (dd, 1H, *J* = 15.6, 4.5 Hz, H-3), 6.19 (dd, 1H, *J* = 15.6, 1.8 Hz, H-2), 4.60 (d, 1H, *J* = 7.0 Hz, NH), 4.45 (app br s, 1H, H-4), 4.03-3.93 (m, 1H, H-5), 3.82 (bs, 1H, OH), 3.76 (s, 3H, OCH_3), 2.82-2.77 (m, 2H, H-6), 1.37 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 166.68 (C-1), 156.89 (*Boc* C=O), 146.20 (C-3), 137.22 (C-1'), 129.06 (2 C:s), 128.68 (2 C:s) (C-2', C-3'), 126.76 (C-4'), 122.23 (C-2), 80.38 [$(CH_3)_3C$], 73.46 (C-4), 56.91 (C-5), 51.66 (OCH_3), 36.14 (C-6), 28.18 (3 C:s) [$(CH_3)_3C$]; IR (KBr) 3353, 1731, 1682 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.58; H, 7.45; N, 4.18.

Methyl (2*R*,3*S*)-3-benzyl-1-*tert*-butoxycarbonyl-2-(2-methoxycarbonyl-(*E*)-ethenyl)-aziridine (8). Compound **6** (3.8 g, 11.3 mmol) was added to a solution of Ph_3P (6.3 g, 24.0 mmol) and diethyl azodicarboxylate (DEAD) (3.8 mL, 24.0 mmol) in THF (230 mL). After refluxing for 0.5 h the solvent was removed in vacuo. Purification by flash chromatography (*n*-pentane:ether 4:1) and recrystallization (1% EtOH in *n*-hexane) gave **8** (3.3 g, 93%) as white needles: HPLC (0.5% EtOH in *n*-hexane), 1.5 mL/min, t_R 7.7 min; mp 75-77 °C; $[\alpha]_D$ = -86.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.27-7.13 (m, 5H, Ph), 6.81 (dd, 1H, *J* = 15.5, 6.4 Hz, H-1'), 6.15 (dd, 1H, *J* = 15.5, 0.93 Hz, H-2'), 3.70 (s, 3H, OCH_3), 3.14 (ddd, 1H, *J* = 6.4, 6.4, 0.93 Hz, H-2), 2.86-2.77 (m, 2H, $PhCH_2$), 2.67-2.58 (m, 1H, H-3), 1.35 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 166.14 (Ester C=O), 161.50 (*Boc* C=O), 142.10 (C-1'), 137.77 (C-1''), 128.69 (2 C:s), 128.50 (2 C:s) (C-2'', C-3''), 126.59 (C-4''), 124.89 (C-2'), 81.68 [$(CH_3)_3C$], 51.73 (OCH_3), 45.29 (C-3), 41.12 (C-2), 34.16 ($PhCH_2$), 27.80 (3 C:s)

[$(CH_3)_3C$]; IR (KBr) 2979, 1718 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_4 \times 0.5\ H_2O$: C, 66.24; H, 7.11; N, 4.29. Found: C, 66.27; H, 7.12; N, 4.17.

Methyl (4*S*,5*S*)-5-[(*tert*-butoxycarbonyl)amino]-4-fluoro-6-phenyl-(*E*)-2-hexenoate (9). Compound **8** (358 mg, 1.13 mmol) was dissolved in CH_2Cl_2 (3 mL) and $SbCl_3$ (8 mg, 0.03 mmol) was added. A white precipitate was immediately formed. Thereafter diethylaminosulfur trifluoride (DAST) (1 mL) was added. After stirring at room temperature for 72 h, water (10 mL) was added to the reaction mixture. The organic phase was separated and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (*n*-pentane:ether 4:1) and recrystallization (1% EtOH in *n*-hexane) gave **9** (136 mg, 36%) as white needles: HPLC (1% EtOH in *n*-hexane), 1.5 mL/min, t_R 5.6 min; mp 74-75 °C; $[\alpha]_D$ = -38.0 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.32-7.23 (m, 5H, Ph), 6.83 (ddd, 1H, *J* = 23.3, 15.7, 3.7 Hz, H-3), 6.08 (ddd, 1H, *J* = 15.7, 2.0, 0.9 Hz, H-2), 5.02 (dddd, 1H, *J* = 46.6, 3.7, 2.0, 0.9 Hz, H-4), 4.69 (bd, 1H, *J* = 10.2 Hz, NH), 4.20-3.99 (m, 1H, H-5), 3.72 (s, 3H, OCH_3), 2.93-2.89 (m, 2H, H-6), 1.38 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 165.88 (C-1), 155.29 (*Boc* C=O), 142.54 (d, *J* = 18.3 Hz, C-3), 136.98 (C-1'), 129.29 (2 C:s), 128.73 (2 C:s) (C-2', C-3'), 126.88 (C-4'), 122.11 (d, *J* = 11.0 Hz, C-2), 90.30 (d, *J* = 179.4 Hz, C-4), 79.91 [$(CH_3)_3C$], 54.24 (d, *J* = 20.8 Hz, C-5), 51.68 (OCH_3), 37.62 (C-6), 28.16 (3 C:s) [$(CH_3)_3C$]; ^{19}F NMR ($CDCl_3$) δ -42.93. IR (KBr) 3368, 2986, 1730, 1665 cm^{-1}. Anal. Calcd for $C_{18}H_{24}FNO_4$: C, 64.1; H, 7.2; N, 4.2. Found: C, 64.3; H, 7.4; N, 4.2.

Methyl (4*R*,5*S*)-5-[(*tert*-butoxycarbonyl)amino]-4-fluoro-6-phenyl-(*E*)-2-hexenoate (10). Compound **11** (48 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and molecular sieves (4Å, 100 mg) were added. Thereafter diethylaminosulfur trifluoride (DAST) (80 μL, 0.6 mmol) was added. After stirring at room temperature for 12 h, water (10 mL) was added to the reaction mixture. The organic phase was separated and the water phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (*n*-pentane:ether 6:1) and recrystallization (1% EtOH in *n*-hexane) gave **10** (42 mg, 83%) as white needles: HPLC (1% EtOH in *n*-hexane), 1.5 mL/min, t_R 6.3 min; mp 69-70 °C; $[\alpha]_D$ = +6.7 (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.30-7.14 (m, 5H, Ph), 6.89 (ddd, 1H, *J* = 22.1, 15.8, 3.5 Hz, H-3), 6.12 (ddd, 1H, *J* = 15.8, 1.8, 0.7 Hz, H-2), 5.18 (app d, 1H, *J* = 48.4 Hz, H-4), 4.59 (d, 1H, *J* = 8.4 Hz, NH), 4.19-4.02 (m, 1H, H-5), 3.74 (s, 3H, OCH_3), 2.87 (dd, 1H, *J* = 15.8, 7.1 Hz, H-6a), 2.79-2.69 (m, 1H, H-6b), 1.32 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 165.95 (C-1), 155.10 (*Boc* C=O), 144.72 (d, *J* = 18.3 Hz, C-3), 136.68 (C-1'), 129.26 (2 C:s), 128.58 (2 C:s) (C-2', C-3'), 126.74 (C-4'), 122.48 (d, *J* = 11.0 Hz, C-2), 92.14 (d, *J* = 180.7 Hz, C-4), 79.94 [$(CH_3)_3C$], 53.97 (d, *J* = 20.8 Hz, C-5), 51.86 (OCH_3), 34.95 (C-6), 28.19 (3 C:s) [$(CH_3)_3C$]; ^{19}F NMR ($CDCl_3$) δ -37.58. IR (KBr) 3025, 1717 cm^{-1}. Anal. Calcd for $C_{18}H_{24}FNO_4 \times 1\ H_2O$: C, 60.83; H, 7.37; N, 3.94. Found: C, 61.04; H, 6.88; N, 3.87.

Methyl (2*S*,3*S*)-3-benzyl-1-*tert*-butoxycarbonyl-2-[2-methoxycarbonyl-(*E*)-ethenyl]-aziridine (11). Compound **7** (3.6 g, 10.7 mmol) was added to a solution of Ph_3P (5.6 g, 21.4 mmol) and DEAD (3.4 mL, 21.4 mmol) in THF (200 mL). After refluxing for 0.5 h the solvent was removed in vacuo. Purification by flash chromatography (*n*-pentane:ether 4:1) gave **11** (3.1 mg, 91%) as a colorless oil: HPLC (0.5% EtOH in *n*-hexane), 1.5 mL/min, t_R 10.6 min; $[\alpha]_D$ = -12.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.28-7.16 (m, 5H, Ph), 6.36 (dd, 1H, *J* = 15.5, 8.9 Hz, H-1'), 6.08 (d, 1H, *J* = 15.5 Hz, H-2'), 3.66 (s, 3H, OCH_3), 3.04 (dd, 1H, *J* =

14.5, 5.0 Hz, $PhCH_{2a}$), 2.89 (dd, 1H, J = 8.9, 2.8 Hz, H-2), 2.74-2.68 (m, 1H, H-3), 2.58 (dd, 1H, J = 14.5, 7.2 Hz, $PhCH_{2b}$), 1.38 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 165.89 (Ester C=O), 159.73 (*Boc* C=O), 143.92 (C-1′), 137.09 (C-1′′), 128.64 (2 C:s), 128.61 (2 C:s) (C-2′′, C-3′′), 126.81 (C-4′′), 124.01 (C-2′), 81.99 [$(CH_3)_3C$], 51.68 (OCH_3), 45.64 (C-3), 43.49 (C-2), 37.23 ($PhCH_2$), 27.89 (3 C:s) [$(CH_3)_3C$]; IR (neat) 2978, 1721 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.06; H, 7.29; N, 4.35.

Methyl (4*S*,5*S*)-5-[(*tert*-butoxycarbonyl)amino]-4-fluoro-6-phenyl-hexanoate (12). Compound **9** (30 mg, 0.09 mmol) was added to a suspension of 10% Pd/C (20 mg) in EtOH (8 mL). After stirring under hydrogen atmosphere at room temperature overnight the catalyst was filtered off through a celite pad washed with EtOH (10 mL). The solvent was removed in vacuo. Purification by flash chromatography (*n*-pentane:ether 5:1) and recrystallization (1% EtOH in *n*-hexane) gave **12** (30 mg, 99%) as white needles; HPLC (1% EtOH in *n*-hexane), 1.5 mL/min, t_R 8.3 min; mp 71-72 °C; $[\alpha]_D$ = -14.4 (*c* 0.61, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.32-7.20 (m, 5H, Ph), 4.70 (bd, 1H, J = 10.3 Hz, NH), 4.45 (dddd, 1H, J = 47.6, 8.8, 3.4, 0.8 Hz, H-4), 4.00-3.86 (m, 1H, H-5), 3.63 (s, 3H, OCH_3), 2.92-2.82 (m, 2H, H-6), 2.43-2.39 (m, 2H, H-2), 2.15-2.02 (m, 1H, H-3a), 1.90-1.73 (m, 1H, H-3b), 1.40 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 173.17 (C-1), 155.58 (*Boc* C=O), 137.40 (C-1'), 129.35 (2 C:s), 128.56 (2 C:s) (C-2', C-3'), 126.60 (C-4'), 92.48 (d, J = 173.3 Hz, C-4), 79.65 [$(CH_3)_3C$], 54.11 (d, J = 18.3 Hz, C-5), 51.62 (OCH_3), 38.60 (C-6), 29.65 (d, J = 4.9 Hz, C-2), 28.28 (3 C:s) [$(CH_3)_3C$], 27.16 (d, J = 20.8 Hz, C-3); ^{19}F NMR ($CDCl_3$) δ -41.18; IR (KBr) 3350, 2963, 1738, 1524 cm^{-1}. Anal. Calcd for $C_{18}H_{26}FNO_4$: C, 63.70; H, 7.72; N, 4.13. Found: C, 63.79; H, 7.58; N, 4.09.

Methyl (4*R*,5*S*)-5-[(*tert*-butoxycarbonyl)amino]-4-fluoro-6-phenyl-hexanoate (13) and Methyl (*S*)-5-[(*tert*-butoxycarbonyl)amino]-6-phenyl-(*E*)-3-hexanoate (14). Compound **10** (30 mg, 0.09 mmol) was added to a suspension of 10% Pd/C (20 mg) in EtOH (8 mL). After stirring under hydrogen atmosphere in room temperature overnight the catalyst was filtered off through a celite pad washed with EtOH (10 mL). The solvent was removed in vacuo. Purification by flash chromatography (*n*-pentane:ether 5:1) and recrystallization (1% EtOH in *n*-hexane) gave **13** (15 mg) and **14** (15 mg) as white needles in a total yield of 99%.

13: HPLC (1% EtOH in *n*-hexane), 1.5 mL/min, t_R 9.3 min; mp 86-88 °C; $[\alpha]_D$ = +22.7 (*c* 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.32-7.19 (m, 5H, Ph), 4.51 (bd, 1H, J = 8.8 Hz, NH), 4.40 (m, 1H, H-4), 3.99 (m, 1H, H-5), 3.69 (s, 3H, OCH_3), 3.00 (dd, 1H, J = 13.9, 4.2 Hz, H-6a), 2.79-2.73 (m, 1H, H-6b), 2.60-2.42 (m, 2H, H-2), 2.05-1.94 (m, 2H, H-3), 1.34 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 173.30 (C-1), 155.14 (*Boc* C=O), 137.04 (C-1'), 129.43 (2 C:s), 128.46 (2 C:s) (C-2', C-3'), 126.54 (C-4'), 93.89 (d, J = 174.6 Hz, C-4), 79.62 [$(CH_3)_3C$], 53.73 (d, J = 23.9 Hz, C-5), 51.73 (OCH_3), 35.44 (C-6), 29.78 (d, J = 3.7 Hz, C-2), 28.22 (3 C:s) [$(CH_3)_3C$], 27.07 (d, J = 20.2 Hz, C-3); ^{19}F NMR ($CDCl_3$) δ -33.69; IR (KBr) 3357, 2964, 1736, 1683 cm^{-1}. Anal. Calcd for $C_{18}H_{26}FNO_4$: C, 63.70; H, 7.72; N, 4.13. Found: C, 63.75; H, 7.72; N, 4.09.

14: HPLC (1% EtOH in *n*-hexane), 1.5 mL/min, t_R 9.9 min; mp 63-64 °C; $[\alpha]_D$ = +12.7 (*c* 1.25, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.32-7.15 (m, 5H, Ph), 4.34 (bd, 1H, J = 8.2 Hz, NH), 3.82 (m, 1H, H-5), 3.64 (s, 3H, OCH_3), 2.82-2.70 (m, 2H, H-6), 2.36-2.22 (m, 2H, H-2), 1.74-1.28 (m, 4H, H-3, H-4), 1.40 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 173.86 (C-1), 155.44 (*Boc* C=O), 138.03 (C-1'), 129.44 (2 C:s), 128.31 (2 C:s) (C-2', C-3'), 126.30 (C-4'), 79.10 [$(CH_3)_3C$], 51.48 (OCH_3), 51.26 (C-5), 41.36 (C-6), 33.62 (C-2), 33.44 (C-4), 28.36 (3 C:s) [$(CH_3)_3C$], 21.38 (C-3); IR (KBr) 3356, 2947, 1736, 1682 cm^{-1}. Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.09; H, 8.45; N, 4.42.

Methyl (4*S*,5*S*)-5-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-6-phenyl-hexanoate (15). Compound **6** (150 mg, 0.45 mmol) was added to a suspension of 10% Pd/C (20 mg) in EtOH (10 mL). After stirring under hydrogen atmosphere at room temperature overnight the catalyst was removed by filtration through a celite pad washed with EtOH (10 mL). The solvent was removed in vacuo. Purification by flash chromatography (*n*-pentane:ether 1:1) and recrystallization (1% EtOH in *n*-hexane) gave **15** (135 mg, 89%) as white needles: HPLC (2.5% EtOH in *n*-hexane), 1.5 mL/min, t_R 11.0 min; mp 113-114 °C; $[\alpha]_D$ = -17.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32-7.18 (m, 5H, Ph), 4.86 (bd, 1H, *J* = 9.1 Hz, NH), 3.72-3.60 (m, 2H, H-5, H-4), 3.65 (s, 3H, OCH_3), 3.01 (bs, 1H, OH), 2.90-2.88 (m, 2H, H-6), 2.52-2.41 (m, 2H, H-2), 1.87-1.70 (m, 2H, H-3), 1.40 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 174.88 (C-1), 156.17 (*Boc* C=O), 138.33 (C-1'), 129.29 (2 C:s), 128.46 (2 C:s) (C-2', C-3'), 126.34 (C-4'), 79.44 [$(CH_3)_3C$], 71.32 (C-4), 56.14 (C-5), 51.77 (OCH_3), 38.49 (C-6), 30.86 (C-2), 29.56 (C-3), 28.30 (3 C:s) [$(CH_3)_3C$]; IR (KBr) 3368, 2986, 1730, 1665 cm^{-1}. Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.04; H, 7.94; N, 4.25.

(4*R*)-4-{1-[(*S*)-(*tert*-Butoxycarbonyl)amino]-2-phenylethyl}-γ-butyrolactone (16). Compound **16** was obtained in 99% yield by hydrogenation of **7** (150 mg, 0.45 mmol) with 10% Pd/C (20 mg) in EtOH (10 mL) as described above for the preparation of **15**. Purification by flash chromatography was performed using *n*-pentane:ether 2:3 as eluent; HPLC (2.5% EtOH in *n*-hexane), 1.5 mL/min, t_R 10.0 min; mp 159-160 °C; $[\alpha]_D$ = -3.9 (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.33-7.22 (m, 5H, Ph), 4.63 (d, 1H, *J* = 10.0 Hz, NH), 4.48 (ddd, 1H, *J* = 7.8, 7.8, 1.5 Hz, H-4), 4.01 (app q, 1H, *J* = 8.8 Hz, H-1'), 2.96 (dd, 1H, *J* = 13.4, 7.1 Hz, H-2'a), 2.88 (dd, 1H, *J* = 13.4, 8.8 Hz, H-2'b), 2.59-2.45 (m, 2H, H-2), 2.16-2.09 (m, 2H, H-3), 1.40 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 177.20 (C-1), 155.83 (*Boc* C=O), 137.14 (C-1''), 129.31 (2 C:s), 128.63 (2 C:s) (C-2'', C-3''), 126.72 (C-4''), 79.88 [$(CH_3)_3C$], 76.52 (C-4), 54.02 (C-1'), 39.37 (C-2'), 28.70 (C-2), 28.21 (3 C:s) [$(CH_3)_3C$], 24.12 (C-3); IR (KBr) 3306, 2985, 1771 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.97; H, 7.57; N, 4.69.

Methyl (5*S*)-5-[(*tert*-butoxycarbonyl)amino]-4-oxo-6-phenyl-hexanoate (17). Compound **5** (100 mg, 0.3 mmol) was added to a suspension of 10% Pd/C (10 mg) in pyridine (5 mL). After stirring under hydrogen atmosphere at room temperature overnight the catalyst was filtered off through a celite pad washed with $CHCl_3$ (10 mL). The solvents were removed in vacuo. Purification by flash chromatography (*n*-pentane:ether 2:1) and recrystallization (1% EtOH in *n*-hexane) gave **17** (77 mg, 77%) as white needles; HPLC (1% EtOH in *n*-hexane), 1.5 mL/min, t_R 12.2 min; mp 66-68 °C; $[\alpha]_D$ = +9.6 (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.33-7.16 (m, 5H, Ph), 5.11 (d, 1H, *J* = 7.3 Hz, NH), 4.53 (app q, 1H, *J* = 7.3 Hz, H-5), 3.66 (s, 3H, OCH_3), 3.13 (dd, 1H, *J* = 11.4, 6.5 Hz, H-6a), 2.94 (dd, 1H, *J* = 11.4, 6.5 Hz, H-6b), 2.78-2.72 (m, 2H, H-3), 2.57 (t, 2H, *J* = 6.5 Hz, H-2), 1.40 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 207.56 (C-4), 173.00 (C-1), 155.32 (*Boc* C=O), 136.40 (C-1'), 129.30 (2 C:s), 128.71 (2 C:s) (C-2', C-3'), 127.02 (C-4'), 79.98 [$(CH_3)_3C$], 60.27 (C-5), 51.86 (OCH_3), 37.54 (C-6), 35.15 (C-3), 28.34 (3 C:s) [$(CH_3)_3C$], 27.62 (C-2); IR (KBr) 3368, 2977, 1710, cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.31; H, 7.45; N, 4.19.

Methyl (5*S*)-5-[(*tert*-butoxycarbonyl)amino]-4,4-difluoro-6-phenyl-hexanoate (18). Compound **17** (100 mg, 0.3 mmol) was added to neat DAST (1.5 mL). After stirring at 55-60 °C for 20 h, ice water (10 mL) was added

to the dark brown reaction mixture. The organic phase was separated and the water phase was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (*n*-pentane:ether 3:1) and recrystallization (1% EtOH in *n*-hexane) gave **18** (50 mg, 47%). HPLC (1% EtOH in *n*-hexane), 1.5 mL/min, t_R 6.8 min; mp 103-105 °C; $[\alpha]_D$ = -5.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.31-7.19 (m, 5H, Ph), 4.50 (bd, 1H, *J* = 10.7 Hz, NH), 4.29-4.18 (m, 1H, H-5), 3.70 (s, 3H, OCH_3), 3.20 (app d, 1H, *J* = 14.6 Hz, H-6a,), 2.68-2.50 (m, 3H, H-2, H-6b), 2.44-2.17 (m, 2H, H-3), 1.28 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 172.74 (C-1), 155.17 (*Boc* C=O), 136.68 (C-1'), 129.20 (2 C:s), 128.41 (2 C:s) (C-2', C-3'), 126.59 (C-4'), 126.34 (t, *J* = 213.6 Hz, C-4), 80.02 [$(CH_3)_3C$], 54.84 (t, *J* = 24.5 Hz, C-5), 51.86 (OCH_3), 34.22 (C-6), 29.44 (t, *J* = 24.4 Hz, C-3), 28.07 (3 C:s) [$(CH_3)_3C$], 26.63 (t, *J* = 4.7 Hz, C-2); ^{19}F NMR ($CDCl_3$) δ -108.75 (ddddd, *J* = 246, 214, 24.5, 24.4, 4.7 Hz), -113.38 (ddddd, *J* = 246, 213.6, 24.5, 24.4, 4.7 Hz); IR (KBr) 3352, 1694, 1520 cm^{-1}. Anal. Calcd for $C_{18}H_{25}F_2NO_4$: C, 60.49; H, 7.05; N, 3.92. Found: C, 60.25; H, 7.06; N, 4.02.

Methyl (5*S*)-5-[(*tert*-butoxycarbonyl)amino]-4,4-difluoro-6-phenyl-(*E*)-hexenoate (19). A solution of LDA was prepared by addition of 1.6 M *n*-butyllithium (0.62 mL, 1 mmol) in hexane to a solution of diisopropylamine (0.2 mL, 1.18 mmol) in dry THF (5 mL) at -78 °C. The reaction mixture was warmed to -5 °C. After 0.5 h the LDA solution was cooled to -78 °C and a solution of **18** (60 mg, 0.17 mmol) in dry THF (1 mL) was added dropwise over 10 min. The reaction mixture was stirred for 1.5 h at -78 °C. PhSeBr (278 mg, 1.18 mmol) in dry THF (1 mL) was added rapidly. The reaction mixture was stirred for 1 h when the mixture was allowed to reach room temperature. The reaction mixture was poured into 1M HCl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated to afford the crude selenyl ester as a light yellow solid, which was used in the next step without further purification.

m-CPBA (204 mg, 1.18 mmol) was added to a solution of the selenyl ester in CH_2Cl_2 (15 mL). After being stirred at room temperature for 20 h the reaction mixture was extracted with saturated aqueous $NaHCO_3$ and brine. The organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (*n*-pentane:ether 8:1) and recrystallization (1% EtOH in *n*-hexane) gave **19** (24 mg, 40%) as white needles. HPLC (1% EtOH in *n*-hexane), 1.5 mL/min, t_R 6.4 min; mp 91-92 °C; $[\alpha]_D$ = -6.3 (*c* 0.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.33-7.18 (m, 5H, Ph), 6.87 (ddd, 1H, *J* = 15.8, 12.8, 11.0 Hz, H-3), 6.34 (app dt, 1H, *J* = 15.8, 2.1 Hz, H-2), 4.52 (bd, 1H, *J* = 9.8 Hz, NH), 4.33 (m, 1H, H-5), 3.78 (s, 3H, OCH_3), 3.18 (dd, 1H, *J* = 14.4, 3.5 Hz, H-6a), 2.67 (dd, 1H, *J* = 14.5, 10.5 Hz, H-6b), 1.28 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 165.21 (C-1), 154.93 (*Boc* C=O), 137.60 (t, *J* = 25.7 Hz, C-3), 136.14 (C-1'), 129.15 (2 C:s), 128.53 (2 C:s) (C-2', C-3'), 126.77 (C-4'), 125.97 (t, *J* = 7.4 Hz, C-2), 119.52 (t, *J* = 246.4 Hz, C-4), 80.22 [$(CH_3)_3C$], 55.24 (t, *J* = 25.7 Hz, C-5), 52.15 (OCH_3), 34.28 (C-6), 28.05 (3 C:s) [$(CH_3)_3C$]; ^{19}F NMR ($CDCl_3$) δ -106.71 (app d, *J* = 249.5 Hz, F_a), -122.45 (app dt, *J* = 249.5, 15.4 Hz, F_b); IR (KBr) 3363, 1724, 1694 cm^{-1}. Anal. Calcd for $C_{18}H_{23}F_2NO_4$: C, 60.83; H, 6.52; N, 3.94. Found: C, 60.93; H, 6.46; N, 3.85.

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