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Synthetic Studies Towards Proline Amide Isosteres, Potentially Useful Molecules for Biological Investigations

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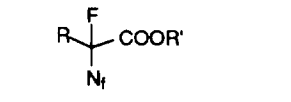
Abstract: 2-Ethenylpyrrolidine derivative **8b** was prepared from *N*-protected proline ethyl ester **6b**. Bromofluorination of **8b** with NBS–Bu_4NF/2HF gave a 1:1 regioisomeric mixture, **9b** and **10b** (X = Br). Dehydrobromination of **9b** and **10b** with *t*-BuOK produced a fluoroolefin **11** and a proline amide isostere model **12**, respectively. Deprotection of the Z group in **12** was attempted by treatment with CF_3COOH. Although formation of the useful molecule in pseudopeptide synthesis, **13**, was observed as checked by NMR spectra, it seemed to decompose slowly during purification procedure to give a mixture of fluorine-free compounds.

INTRODUCTION

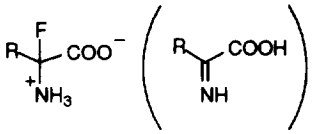
It is well known that fluorination of organic compounds often induces new physical, chemical, and biological properties.[1] Introduction of fluorine atoms into biochemically significant molecules has been an important strategy in the development of useful analogues of such classes of steroids, amino acids, sugars, *etc.*, particularly with respect to physiological and pharmaceutical applications.[2] Among the many fluorinated amino acids synthesized,[3] there are however no reports of α-fluoro-α-amino acids, undoubtedly a reflection of the inherent chemical instability of a geminally substituted fluoro-amino moiety. Nevertheless, introduction of a fluorine atom into the α position of α-amino acids would inevitably influence both physical and chemical properties of the parent molecules and further, the α-fluorinated amino acids, when linked as peptides, would necessarily result in the alteration of conformation of the whole molecules. Despite expected difficulties due to the high reactivity of this type of structure, we felt proper manipulation of structural features might permit the isolation of such analogues.

During our continuing studies on approaches to α-fluoro-α-amino acid derivatives, some protected α-fluoro-α-amino acid derivatives **1**[4] and their potential precursors **2**[5] and **3**[6] were successfully prepared. However, we failed to isolate the α-fluoro-α-amino acid **4** itself, due to its inherent character of being subjected readily to dehydrofluorination, with formation of the unstable imine compounds.[7] In order to overcome this problem, we considered the introduction of a fluorine atom into the α position of proline derivatives **5**.[8] Proline is the only proteinogenic α-amino acid which loses the amidic proton when acylated through a peptide bond. Therefore, dehydrofluorination may occur less readily with the *N*-protected α-fluoroproline moiety. However, attempted direct fluorination either of the *N*-protected proline methyl

esters[9] with electrophilic fluorination agents[10,11] or of the corresponding enol ethers with diluted fluorine gas,[12] did not give the desired compounds **5**. These results might be ascribed to the difficulty both in generating the unstable carbanions and in converting into the enol ethers.



1: $N_f = N(COOR')_2$, R = R' = H
2: $N_f = NO_2$, R' = Et
3: $N_f = N_3$, R' = Et



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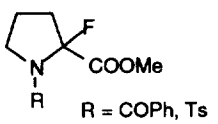

R = COPh, Ts

5

We next focused our attention on the fluorine-containing proline amide isosteres,[13,14] which seemed of special interest from viewpoint of non-proteinogenic amino acid equivalents. Here we present preliminary results on the design and synthetic studies of such molecules. Our immediate interest was to determine the chemical stability of such molecules as well as to investigate their biochemical applications. In this work, ^{19}F NMR techniques served as powerful probes in chemical synthesis, especially in solving the problem of rotational isomers.

RESULTS AND DISCUSSION

Since the introduction of a fluorine atom into the α position of α-amino acids seemed difficult, even as a protected form in a peptide chain, we considered the preparation of the proline amide isostere model **12**[13,14] and the potentially useful building block **13** in proline-containing pseudopeptide synthesis. Compound **13** is of special interest as a non-proteinogenic component when incorporated at the C-terminal site or any other appropriate site of oligopeptides, *e.g.*, TRH and LH-RH.[14]

Reaction of *N*-(*t*-butoxycarbonyl)-(*L*)-proline ethyl ester (**6a**) with DIBAL-H gave the aldehyde **7a**, which reacted with methylenetriphenylphosphorane to produce the olefin **8a** in moderate yield. Each proton of **8a** appears broadly in the shape in the ^1H NMR spectra, which indicated the presence of rotational isomers relating to the C—N bond axis in the urethane moiety. Halofluorination of **8a** was attempted using DBH-Et_4NF/4HF, NBS–Py/$(HF)_n$,[15] NBS–Et_3N/3HF,[16,17] IPy_2BF_4–HBF_4,[18] NIS or DBH–Bu_4NF/2HF,[19] and I_2–AgF,[20] however, the yields of the adducts **9a** and/or **10a** (X = Br or I) were very poor in most cases due to the formation of a complicated mixture. We ascribed these results to the presence of the acid-sensitive *t*-butoxycarbonyl (*t*-Boc) group. We then swiched to the *N*-benzyloxycarbonyl (Z) derivative **8b**, which was prepared readily from **6b** in an analogous manner. Among various methods employed for halofluorination mentioned above, we were unable to effect the fluoroiodination of **8b**. Only bromofluorination proceeded, as checked by ^1H and ^{19}F NMR spectra, although the yield of the desired compound **9b** seemed too low to isolate it.

We next applied a modification of the Hiyama procedure[19] to **8b**, a procedure which employs NBS instead of NIS or DBH. Reaction of **8b** with NBS–Bu_4NF/2HF in CH_2Cl_2 at 0 °C produced a 1:1 mixture of the regioisomers **9b** and **10b** (X = Br) in 21% yield and each isomer was isolated after repeated chromatography. Each consisted of a diastereomeric mixture as revealed by the ^{19}F NMR spectra, *i.e.*, *ca.* 2:1 intensity ratio δ at −191.0 (dtd, J = 42.3, 22.5, 22.5 Hz) and −190.0 (dtd, J = 44.1, 22.7, 22.7 Hz) ppm from $CFCl_3$ for **9b** and *ca.* 2:1 ratio δ at −213.7 (td, J = 46.9, 16.6 Hz) and −211.6 (td, J = 46.5, 14.7 Hz)

ppm for **10b**, respectively. The fluorine signals for **10b** with the above shown splitting pattern could be assigned for the structure of *exo*-fluorinated isomers, although this type of reaction is expected to give *endo* isomers predominantly, based on mechanistic considerations.[16] The presence of *exo*-fluorinated isomers was also supported by the NMR spectra of the 1:1 isomeric mixture of *E*-fluoroolefins **11** [^{19}F NMR δ at −131.7 (dd, J = 85.8, 18.4 Hz) and −130.8 (dd, J = 83.7, 18.4 Hz) ppm;[21] ^{1}H NMR H^a proton δ at 5.30 (1H, ddd, $J_{Ha-F(cis)}$ = 18.7, $J_{Ha-Hb(trans)}$ = 11.0, J_{Ha-Hc} = 7.7 Hz) ppm], obtained by treatment of **10b** with *t*-BuOK. Those two fluorine signals with the same splitting pattern, which appeared very closely in the chemical shift, clearly indicated the presence of two isomers, although both of them could be assigned to *E*-geometric compounds from the coupling constants in the ^{1}H and ^{19}F NMR spectra. Therefore, the two fluorine signals observed may reasonably be ascribed to the presence of two rotational isomers, as is discussed below. After investigations, we were finally unable to find reaction conditions to suppress the formation of the unwanted isomer **10b**.

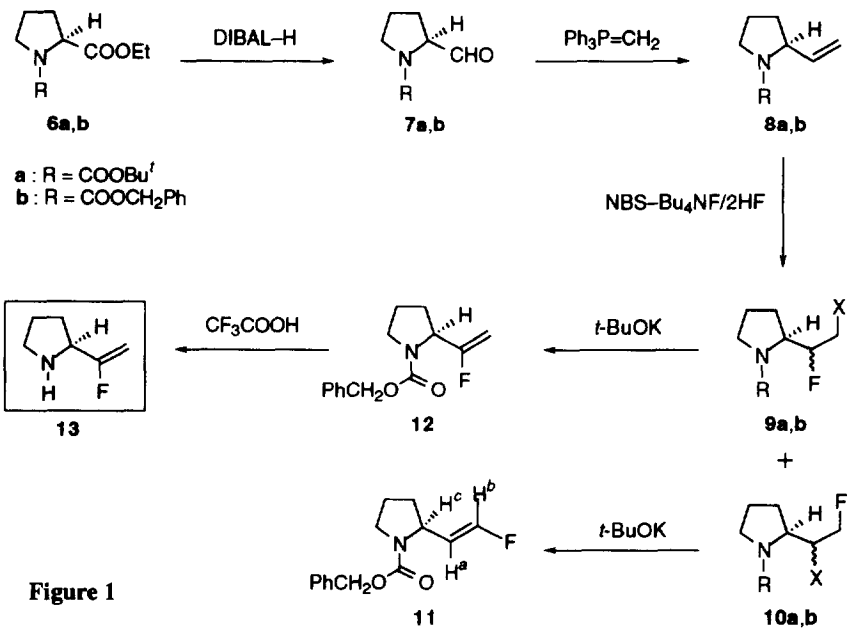

Figure 1

Dehydrobromination of a mixture of **9b** and **10b** (X = Br) was achieved by treatment with *t*-BuOK in Et_2O to yield again *ca.* 1:1 mixture of fluoroolefins in 59% yield and the two regioisomeric isomers **11** and **12** were isolated after repeated chromatography. The ^{19}F NMR spectrum of **12** revealed two kinds of fluorine signals with 1:1 intensity ratio δ at −110.4 (ddd, J = 49.7, 15.0, 15.0 Hz) and −109.0 ppm (ddd, J = 49.6, 17.0, 11.0 Hz), which indicated a mixture of two rotamers, due to the presence of both the bulky *N*-protective Z group and the fluoroolefin side chain. The presence of the two rotational isomers was also supported by ^{1}H NMR spectra of **12**, where all of the proton signals appeared in broadened shape, as was also observed in the case of **8a** and **8b**.

Finally, deprotection of the Z-group in **12** was attempted employing Pd/C–H_2, $Pd(OH)_2$–H_2,[22] Raney Ni T-1,[23] TMSI,[24] HBr/AcOH,[25] HF/Py,[26] KOH,[27] and $Pd(OAc)_2$/Et_3SiH.[28] However, all the reactions

resulted in either formation of defluorinated compounds or recovery of the starting material. After intensive investigation of deprotection conditions, we found that reaction of **12** with CF_3COOH[29] produced the target molecule **13** in *ca.* 50% yield as determined by ^1H NMR, which was accompanied by fluorine-free compounds. The structure of **13** was supported by ^{19}F NMR data of a crude sample, *i.e.*, δ at −108.1 ppm (ddd, J = 49.6, 15.7, 15.7 Hz). To our great disappointment, however, this compound seemed to decompose slowly during purification procedure of neutral alumina chromatography, finally to give a mixture of completely defluorinated compounds, of which ^1H NMR spectra showed no more olefinic proton signals (Figure 1).

In order to verify the inherent instability due to the 2-ethenylpyrrolidine structure,[30] we next attempted *t*-Boc-group deprotection of **8a** under the same reaction conditions using CF_3COOH as above. The amount of the crude product obtained after work-up was rather small and furthermore, no more olefinic protons were observed in the ^1H NMR spectra of the product.

During our synthetic studies, we relied heavily on ^{19}F NMR spectroscopy to determine composition of product mixtures, and structure elucidation. Although we have succeeded in obtaining the model compound for the proline amide isostere **12**, we failed to isolate the potential building block **13** for the moment. There might be room left for challenges to obtain **13** with extensive investigations of reaction conditions and isolation conditions. Since *N*-protected 2-ethenylpyrrolidines such as **12** seem fairly stable, we are now undertaking studies on the preparation of those molecules in which the building block **13** is suitably protected with some α-amino acid derivatives.

EXPERIMENTAL

General. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. ^1H NMR spectra were measured in $CDCl_3$ with Me_4Si as internal standard and were recorded on a Varian Gemini 300 (300 MHz), JEOL GX-270 (270 MHz), or JEOL PMX-60 (60 MHz) spectrometer. ^{19}F NMR spectra were measured in $CDCl_3$ with $CFCl_3$ as internal standard and were taken with a JEOL GX-270 (254 MHz) spectrometer. Upfield shifts are quoted as negative δ values. Mass spectra (EI mode) were taken with a JEOL JMS-D300 or JEOL JMS-AX505HAD spectrometer. Column chromatography and preparative TLC were performed on Kieselgel 60 (Merck, Art. 9385 and 7748, respectively).

Preparation of Ethyl *N*-(2,2-Dimethylethoxycarbonyl)-(*L*)-prolinate (6a): To a solution of (*L*)-proline (10 g, 87 mmol) in EtOH (150 mL) was introduced enough amount of hydrogen chloride gas and the resulting solution was heated at reflux for 1 h. Evaporation of the solvent gave ethyl (*L*)-prolinate hydrochloride (15.6 g, 100%) as a colorless oil. To a suspension of the hydrochloride (13 g, 70 mmol) in $CHCl_3$ (150 mL) were added $NaHCO_3$ (5.9 g), NaCl (14 g), and H_2O (100 mL). To the stirred mixture was added a solution of $(t\text{-Boc})_2O$ (15 g, 70 mmol) in $CHCl_3$ (5 mL) and the whole was heated at reflux for 1.5 h. After cooling, the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (100 mL x 2) and the combined organic layer was dried on $MgSO_4$. Evaporation of the solvent gave an oil, which was chromatographed on silica gel (hexane:AcOEt = 3:1) to give **6a** (8.5 g, 50%) as a colorless oil; IR (neat) 2978 (CH_2), 1744 (COOEt), 1702 (OCON), 1400 and 1367 (*t*-Bu) cm^{-1}; ^1H NMR (300 MHz) δ 1.28 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.42 (9H, s, *t*-Bu), 1.80—2.29 (4H, m, CH_2-CH_2-CH_2N), 3.34—3.60 (2H, m,

CH_2N), 4.12—4.33 (1H, m, CH), 4.17 (2H, q, J = 7.1 Hz, CH_2CH_3); mass spectrum *m/z* 243 (M^+), 170 (M^+ – COOEt), 142 (M^+ – $COOBu^t$), 114 (M^+ – $COOBu^t$ – CH_2=CH_2), 70 (M^+ – CH=CH_2 – CO_2 – $COOBu^t$), 57 (t-Bu^+).

Preparation of Ethyl *N*-(Phenylmethoxycarbonyl)-(*L*)-prolinate (6b): To a solution of (*L*)-proline (9.21 g, 80 mmol) in 1*N* NaOH (160 mL) was added Z-Cl (13.65 g, 80 mmol) with stirring and cooling in an ice-bath and the mixture was stirred at room temperature for 13.5 h. The mixture was acidified with concentrated hydrochloric acid (80 mL) and extracted with AcOEt (150 mL x 3) and the extract was dried on $MgSO_4$. Evaporation of the solvent gave crude Z-(*L*)-proline (20 g, 100%) as a colorless oil. To a solution of Z-(*L*)-proline (12.5 g, 50 mmol) in EtOH (80 mL) was added (+)-10-camphorsulfonic acid (0.15 g, 0.65 mmol) and the mixture was heated at reflux for 20 h. Evaporation of the solvent gave a residue, which was dissolved in AcOEt (100 mL). The solution was washed with saturated $NaHCO_3$ (80 mL) and saturated NaCl (50 mL) and dried on $MgSO_4$. Evaporation of the solvent gave **6b** (13.85 g, 100%) as a colorless oil; IR (neat) 2980—2881 (CH_2), 1743 (COOEt), 1708 (ROCON), 1415 (OCH_2Ph) cm^{-1}; ^1H NMR (300 MHz) δ 1.26 and 1.27 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.80—2.33 (4H, m, CH_2-CH_2-CH_2N), 3.43—3.68 (2H, m, CH_2N), 3.97—4.14 (2H, m, CH_2CH_3), 4.32 (0.5H, dd, J = 3.0, 4.4 Hz, CH), 4.38 (0.5H, dd, J = 4.3, 3.9 Hz, CH), 5.06, 5.16 (1H, ABq, J = 13.5 Hz, CH_2Ph), 5.12, 5.18 (1H, q, J = 13.7 Hz, CH_2Ph), 7.27—7.39 (5H, m, Ph); mass spectrum *m/z* 277 (M^+), 204 (M^+ – COOEt), 160 (M^+ – COOEt – CO_2), 142 (M^+ – $COOCH_2Ph$), 91 ($PhCH_2^+$).

General Procedure for Preparation of *N*-Alkoxycarbonyl-(*L*)-prolinals (7a and 7b): To a chilled solution (–78 °C) of ethyl ester **6a** or **6b** (35 mmol) in CH_2Cl_2 (80 mL) was added dropwise DIBAL–H (1.01 *M* toluene solution, 69 mL) over a period of 25 min and the solution was stirred below –70 °C for 1 h. Reaction was quenched by adding acetone (5 mL) and saturated NH_4Cl (20 mL) and the resulting mixture was allowed to warm to room temperature and stirred at room temperature for 40 min. The mixture was filtered through a pad of celite and the filtrate was washed with saturated NaCl (20 mL) and dried on $MgSO_4$. Evaporation of the solvent gave an oil, which was chromatographed on silica gel (hexane:AcOEt = 3:1) to give **7a** (4.4 g, 63%) or **7b** (3.8 g, 47%).

***N*-(2,2-Dimethylethoxycarbonyl)-(*L*)-prolinal (7a)**: as a colorless oil; ^1H NMR (60 MHz) δ 1.47 (9H, s, t-Bu), 1.80—2.13 (4H, m, CH_2-CH_2-CH_2N), 3.37—3.67 (2H, br m, CH_2N), 4.00—4.40 (1H, br m, CH), 9.50—9.80 (1H, br m, CHO).

***N*-(Phenylmethoxycarbonyl)-(*L*)-prolinal (7b)**: as a colorless oil; IR (neat) 2956 (CH_2), 1734 (CHO), 1700 (OCON), 1415 (OCH_2Ph) cm^{-1}; ^1H NMR (300 MHz) δ 1.53—2.10 (4H, m, CH_2-CH_2-CH_2N), 3.43—3.63 (2H, m, CH_2N), 4.15—4.33 (1H, m, CH), 5.03—5.23 (2H, m, CH_2Ph), 7.20—7.46 (5H, m, Ph); mass spectrum *m/z* 233 (M^+), 234 (M^+ + 1), 204 (M^+ – CHO), 160 (M^+ – CHO – CO_2), 114 (M^+ – CHO – CH_2Ph + 1), 91 ($PhCH_2^+$).

General Procedure for Preparation of Alkyl (*S*)-2-Ethenylpyrrolidine-1-carboxylates (8a and 8b): To a stirred and chilled (–78 °C) suspension of methyltriphenylphosphonium bromide (44 mmol) in dry THF (250 mL) was added dropwise BuLi (1.69 *M* solution in hexane, 26 mL) under nitrogen atmosphere over a period of 1 h and was then added dropwise a solution of **7a** or **7b** (22 mmol) in THF (20 mL) over a period of 10 min. The mixture was allowed to warm to room temperature and quenched with water (100 mL) and concentrated. The residue was extracted with AcOEt (100 mL x 3) and the extract was dried on $MgSO_4$. Evaporation of the solvent gave an oil, which was chromatographed on silica gel (hexane:AcOEt

= 4:1) to give **8a** (2.2 g, 50%) or **8b** (0.8 g, 15%).

2,2-Dimethylethyl (*S*)-2-Ethenylpyrrolidine-1-carboxylate (8a): as a colorless oil; IR (neat) 2975—2877 (CH_2), 1697 (OCON), 1394 and 1365 (*t*-Bu), 988 and 914 (RCH=CH_2); ^{1}H NMR (300 MHz) δ 1.4 (9H, s, *t*-Bu), 1.63—2.09 (4H, m, C*H*$_2$-C*H*$_2$-CH_2N), 3.29—3.45 (2H, br m, CH_2N), 4.17—4.43 (1H, br m, CH), 4.92—5.13 (2H, br d, CH=C*H*$_2$), 5.64—5.83 (1H, br m, C*H*=CH_2); mass spectrum *m/z* 197 (M^+), 97 (M^+ – COOBu^t + 1), 57 (*t*-Bu$^+$).

Phenylmethyl (*S*)-2-Ethenylpyrrolidine-1-carboxylate (8b): as a colorless oil; IR (neat) 2974 and 2879 (CH_2), 1701 (OCON), 1412 (OCH_2Ph), 987 and 915 (RCH=CH_2) cm^{-1}; ^{1}H NMR (300 MHz) δ 1.60—2.10 (4H, m, C*H*$_2$-C*H*$_2$-CH_2N), 3.33—3.57 (2H, br m, CH_2N), 4.30—4.50 (1H, br m, CH), 4.93—5.23 (4H, m, C*H*$_2$Ph and RCH=C*H*$_2$), 5.66—5.86 (1H, br m, RC*H*=CH_2), 7.23—7.46 (5H, br m, Ph); mass spectrum *m/z* 231 (M^+), 91 ($PhCH_2^+$).

Reacton of Phenylmethyl (*S*)-2-Ethenylpyrrolidine-1-carboxylate (8b) with NBS–Bu$_4$NF/2HF: To a solution of olefin **8b** (284 mg, 1.23 mmol) and Bu$_4$NF/2HF (551 mg, 1.84 mmol) in CH_2Cl_2 (2 mL) was added *N*-bromosuccinimide (327 mg, 1.84 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 10 h. Water (5 mL) was added and the reaction mixture was transferred into a separatory funnel with CH_2Cl_2 (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 mL x 2). The combined organic layer was dried on $MgSO_4$. Evaporation of the solvent gave a residue, which was fractionated by silica gel column chromatography (hexane:Et_2O = 4:1) to afford a mixture of **9b** and **10b** (86 mg, 21%). Repeated preparative TLC (hexane:Et_2O = 3:1) gave analytical samples of **9b** and **10b**.

Phenylmethyl (2*S*)-2-(2-Bromo-1-fluoroethyl)pyrrolidine-1-carboxylates (9b): as a colorless oil; IR (neat) 2958 (CH_2), 1701 (OCON), 1412 (OCH_2Ph), 1114 (CF), 751 (CBr) cm^{-1}; ^{1}H NMR (300 MHz) δ 1.83—2.17 (4H, m, C*H*$_2$-C*H*$_2$-CH_2N), 3.32—3.62 (4H, br m, CH_2N and CH_2Br), 4.09—4.16 (1H, br m, CHN), 4.73—5.10 (1H, br m, CHF), 5.15 (2H, s, C*H*$_2$Ph), 7.27—7.38 (5H, m, Ph); ^{19}F NMR δ –190.03 (dtd, *J* = 44.1, 22.7, 22.7 Hz) and –190.99 (dtd, *J* = 42.3 22.5, 22.5 Hz) with 1:2 signal intensity; mass spectrum *m/z* 329, 331 (M^+), 250 (M^+ – Br), 204 (M^+ – $CHFCH_2Br$).

Phenylmethyl (2*S*)-2-(1-Bromo-2-fluoroethyl)pyrrolidine-1-carboxylates (10b): as a colorless oil; IR (neat) 2957 (CH_2), 1700 (OCON), 1411 (OCH_2Ph), 1111 (CF), 770 (CBr) cm^{-1}; ^{1}H NMR (300 MHz) δ 1.77—2.15 (4H, m, C*H*$_2$-C*H*$_2$-CH_2N), 3.34—3.71 (2H, m, CH_2N), 4.13 (1H, br ddd, *J* = 11, 6.6, 1.1 Hz, CHN), 4.31—4.76 (3H, m, CHBr and CH_2F), 5.13 and 5.18 (2H, ABq, 12.6 Hz, C*H*$_2$Ph), 7.29—7.38 (5H, m, Ph); ^{19}F NMR δ –211.63 (td, *J* = 46.5, 14.7 Hz) and –213.73 (td, *J* = 46.9, 16.6 Hz) with 1:2 signal intensity; mass spectrum *m/z* 329, 331 (M^+), 250 (M^+ – Br), 204 (M^+ – $CHFCH_2Br$).

Dehydrobromination of Phenylmethyl (2*S*)-2-(1,2-Dihalogenoethyl)pyrrolidine-1-carboxylates 9b and 10b with *t*-BuOK: To a solution of a mixture of *vic*-bromofluoroalkanes **9b** and **10b** (18 mg, 0.055 mmol) in Et_2O (0.11 mL) was added potassium *t*-butoxide (9.0 mg, 0.08 mmol) and the mixture was stirred at 0 °C for 2.5 h. Water (3 mL) and Et_2O (2 mL) were added to the mixture and the whole was transferred into a separatory funnel and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 mL x 2) and the combined organic layer was dried on $MgSO_4$. Evaporation of the solvent gave a residue, which was fractionated by silica gel preparative TLC (hexane:Et_2O = 2:1) to give a mixture of olefinic compounds **11** and **12** (8 mg, 59%). Repeated preparative TLC under the same conditions produced analytical samples of **11** (3 mg) and **12** (3 mg).

Phenylmethyl (*S*)-2-[2-Fluoro-(*E*)-ethenyl]pyrrolidine-1-carboxylate (11): as a colorless oil; IR (neat) 2954 (CH_2), 1701 (OCON), 1674 (CH=CHF), 1411 (OCH_2Ph), 1100 (CF) cm^{-1}; ^1H NMR (300 MHz) δ 1.69—2.08 (4H, m, CH_2-CH_2-CH_2N), 3.38—3.47 (2H, br m, CH_2N), 4.31—4.37 (1H, br m, CHN), 5.15 and 5.19 (2H, ABq, 12.1 Hz, CH_2Ph), 5.30 (1H, ddd, J = 18.7, 11.0, 7.7 Hz, CH=), 6.32—6.89 (1H, m, CHF), 7.28—7.37 (5H, m, Ph); ^{19}F NMR δ −130.75 (dd, J = 83.7, 18.4 Hz) and −131.69 (dd, J = 85.8, 18.4 Hz); mass spectrum *m/z* 249 (M^+), 114 ($M^+ - COOCH_2Ph$).

Phenylmethyl (*S*)-2-(1-Fluoroethenyl)pyrrolidine-1-carboxylate (12): as a colorless oil; IR (neat) 2954 (CH_2), 1712 (OCON), 1678 ($CF=CH_2$), 1410 (OCH_2Ph), 1114 (CF) cm^{-1}; ^1H NMR (300 MHz) δ 1.85—2.08 (4H, m, CH_2-CH_2-CH_2N), 3.39—3.57 (2H, m, CH_2N), 4.22—4.69 (3H, br m, CHN and $CF=CH_2$), 5.14 (2H, s, CH_2Ph), 7.34—7.37 (5H, m, Ph); ^{19}F NMR δ −108.97 (ddd, J = 49.6, 17.0, 11.0 Hz) and −110.36 (ddd, J = 49.6, 15.0, 15.0 Hz); mass spectrum *m/z* 249 (M^+), 114 ($M^+ - COOCH_2Ph$).

Reaction of (*S*)-2-(1-Fluoroethenyl)pyrrolidine-1-carboxylate (12) with CF_3COOH: A solution of *N*-Z-derivative **12** (19 mg, 0.076 mmol) in CF_3COOH (0.3 mL) was stirred at room temperature for 18 h. Water (2 mL) and CH_2Cl_2 (2 mL) were added to the solution and the whole was transferred into a separatory funnel and the organic layer was separated. The aqueous layer was basified with 1*N* NaOH and extracted with AcOEt (5 mL x 3) and the extract was dried on K_2CO_3. Evaporation of the solvent gave a crude product of **13**.; ^1H NMR (270 MHz) δ 1.52 (1H, s, NH), 1.71—2.08 (4H, m, CH_2-CH_2-CH_2N), 2.96—3.15 (2H, m, CH_2N), 3.44—3.52 (1H, m, CHN), 4.33—4.80 (2H, m, $CF=CH_2$); ^{19}F NMR δ −108.11 (ddd, J = 49.7, 15.7, 15.7 Hz); mass spectrum *m/z* 115 (M^+). Attempted purification with alumina column chromatography (AcOEt) gave a complicated mixture, as checked by ^1H and ^{19}F NMR spectra.

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