Synthetic Studies for Novel Structure of α-Nitrogenously Functionalized α-Fluorocarboxylic Acids. Part 1. The First Synthesis and Reactions of *N*-Protected α-Fluoroglycines

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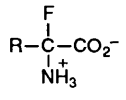
The first synthesis of the *N*-protected α-fluoro-α-amino acid esters **12**, **13**, **21** and **22**, and the corresponding acids **16** and **24**, is described. Reaction of ethyl and t-butyl bromofluoroacetates **4** and **9** with di-t-butyl and dibenzyl iminodicarboxylate potassium salts **10c** and **20b** gave the fluoroglycine derivatives **12**, **13**, **21** and **22**, respectively. Hydrolysis of the ethyl ester **12** and the t-butyl ester **22** successfully afforded the key compounds *N*,*N*-di(t-butoxycarbonyl)-α-fluoroglycine **16** and *N*,*N*-di(benzyloxycarbonyl)-α-fluoroglycine **24**. Conversion into the novel structure of α-fluoroglycine itself (**1**; R = H) by acidic *N*-deprotection of compound **16** or hydrogenative debenzylation of compound **24**, however, failed to produce any decomposition products associated with dehydrofluorination.

Following recent rapid progress in studies on the synthesis and reactions of organofluorine compounds, many attempts have been made to introduce a fluorine atom into biologically significant molecules such as sugars and steroids.[1] There have also been quite a few attempts at chemical[2] and enzymatic[3] syntheses and biological activity examination[4] of fluorine-containing α-amino acids in anticipation of the inherent chemical properties and activities[5] caused by the introduction of a fluorine atom. However, no compounds have been reported where fluorine (or any other halogen atom) is introduced into the α-position (*i.e.*, on the chiral centre) of any α-amino acid. The reason for this seems to be the inherent instability of the geminally halogenated amine moiety, which easily dehydrohalogenates to form another unstable structure – an imine. The α-amino-α-halogeno acids are therefore significant not only as modified bioactive compounds but also from a structural chemistry viewpoint, although they are small molecules.



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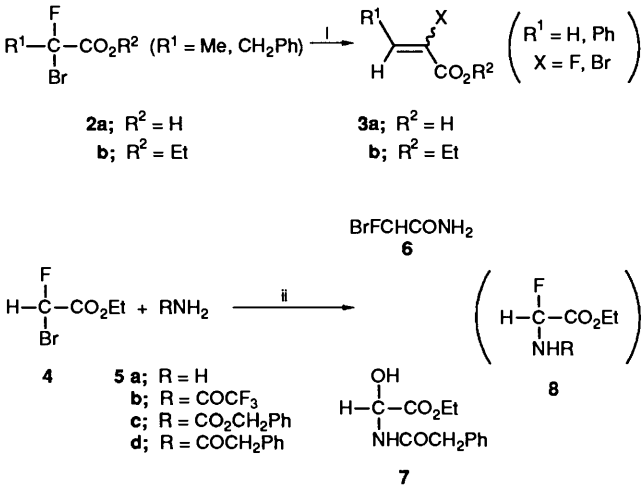
We thought the α-fluoro-α-amino acid structure **1** might be capable of existing under certain controlled conditions because of the general strength of the C–F bond, as evidenced by the meagre leaving ability of fluoride ion compared with the other halide ions. There had been, however, no published syntheses of any α-nitrogenously functionalized α-fluorocarboxylic acid derivatives before we first reported our preliminary work.[6] We here describe a full account of the synthetic details of the preparation of this new class of fluorine compounds and our attempted construction of the novel α-fluoro-α-amino acid structure **1**.

Results and Discussion

Since both selective monofluorination[7] at the α carbon of protected amino acid derivatives and electrophilic amination† of 2-fluoro esters seemed very difficult, we attempted nucleophilic introduction of the amino functionality into 2-fluoro esters. Ammonolysis of 2-bromo-2-fluorocarboxylic acids **2a** or esters **2b**, prepared from the corresponding α-amino esters,[10] produced mixtures of undesired dehydrohalogenated products **3a** or **3b**. In order to avoid the problem of elimination, we next examined the simplest structure of the clan, namely ethyl bromofluoroacetate **4**. Reaction of compound **4** with ammonia **5a** or the protected amine derivatives **5b–d**[11] in the presence of an appropriate base, however, did not give the desired compounds **8**, yielding instead mainly bromofluoroacetamide (**6**)[12] from substrates **5a–c** and defluorination product **7** from **5d**, respectively, probably due to the instability of the metal amide nucleophiles or the high reactivity of the products (Scheme 1).

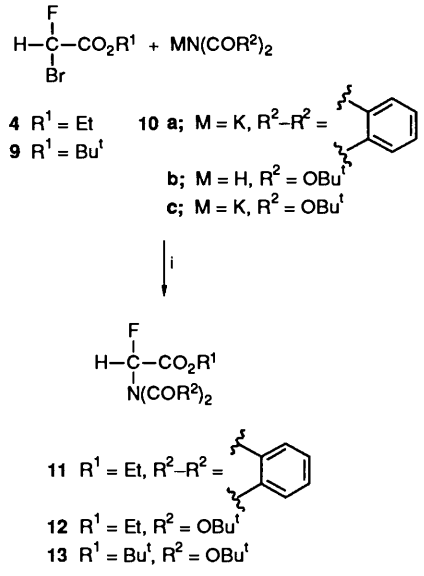


Scheme 1 *Reagents:* i, NH_3, EtOH; ii, NaH, KH, KOBu^t, or LDA, THF or EtOH

Our next attempt at the introduction of nitrogenous functionality onto the fluorine-bearing carbon focused on Gabriel's method.[13] Reaction of bromo ester **4** with potassium phthalimide **10a** in heated *N*,*N*-dimethylformamide (DMF) successfully produced the first α-fluorinated α-amino acid derivative, *N*-phthaloyl-α-fluoroglycine ethyl ester **11**.[6] However, application of the rather vigorous conditions required for removal of the phthaloyl group[14] and also for cleavage of the

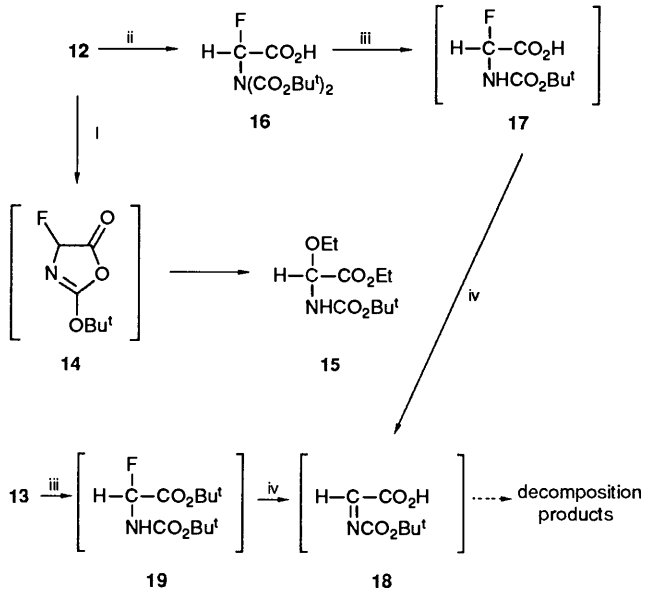
† Electrophilic amination using various reagents[8] was unsuccessful presumably due to the difficulty of generating α-fluorocarbanions.[9]

ester linkage[15,16] to product **11** damaged the C–F bond. In the course of considering much more gentle deprotective conditions adaptable to later stages of our synthetic strategy, we chose di-t-butyl iminodicarboxylate **10b** as an amino functionality, which was prepared easily from t-butyl oxamate according to the method[17] of Jones. Condensation of the potassium salt **10c** with the ethyl ester **4** and the corresponding t-butyl ester **9**[18] in DMF gave the fluoroglycine derivatives **12** and **13**, respectively, in good yield (Scheme 2).



Scheme 2 *Reagents and conditions:* i, DMF, 90–120 °C (72–89% yield)

The key compounds **12** and **13** now being to hand, we started to investigate their possible construction into the novel α-fluoro amino acid structure (**1**; R = H). The well known C–F bond stability was also a matter of interest in our case.[19] Acidic cleavage of the amino protective group of compound **12** with CF_3CO_2D resulted in the formation of defluorinated products **15**, presumably *via* the oxazolone intermediate **14**. Therefore, cleavage of the ester moiety prior to deprotection of the amino group seemed indispensable to maintain the fluorine atom. Saponification of the ethyl ester **12** with 5% NaOH was accomplished smoothly, happily without the anticipated defluorination, to afford the *N*-protected α-fluoroglycine **16** in excellent yield. The final process was attempted by treatment of compound **16** with a catalytic amount of CF_3CO_2D or HF in $CDCl_3$ as monitored by ^1H and ^{19}F NMR spectroscopy. One of the two carboxylates protecting the amino group was cleaved easily to form the unstable *N*-t-butoxycarbonyl-α-fluoroglycine **17**.* However, prolonged exposure of compound **17** to an excess of acidic media (HF in $CDCl_3$), in expectation of complete deprotection, seemed unsatisfactory. Decomposition of compound **17** under acidic media *via* the *N*-carboxyimine structure **18** could be the possible reason.† Similar acid-treatment of t-butyl ester **13** resulted in the formation of the partially deprotected t-butyl ester **19** as evidenced by NMR spectroscopy, which upon application of the stronger acidic conditions produced the same compound **18** (Scheme 3).



Scheme 3 *Reagents and conditions:* i, CF_3CO_2D, $CDCl_3$; ii, 5% NaOH, EtOH (92% yield); iii, catalytic amount of CF_3CO_2D or HF, $CDCl_3$; iv, excess of HF, $CDCl_3$

From these results, application of acidic conditions for the removal of the *N*-protective group at the final step seemed unfavourable because we anticipated that protonation on the fluorine atom would accelerate dehydrofluorination. Free amine generation and concomitant zwitterion formation (as depicted by structure **1**) should be necessary at the final stage since carboxylate ion formation would suppress deprotonation of the amino group which could be the initial stage of dehydrofluorination. In considering these results, we decided that neutral conditions for *N*-deprotection such as hydrogenative deprotection at the final stage would probably be the only way in which we might accomplish our synthesis. Neutral conditions would also be helpful in the work-up procedure so that the target compound could be isolated without tedious manipulation.

It was now necessary to obtain the benzyl analogue **20a**, which Jones reported[17] as being so difficult to prepare. After several attempts, including the unsuccessful application of a modified published procedure,[20] we finally found a simple reaction to obtain compound **20a**. Reaction of benzyl carbamate with benzyl chloroformate in the presence of an equimolar amount of potassium hydride produced target compound **20a** in 64% yield.‡ The dibenzyl iminodicarboxylate **20a** was treated with aqueous KOH to afford the potassium salt **20b**. Introduction of the new amino functionality **20b** into bromo esters **4** and **9** was achieved satisfactorily, under conditions similar to the preparation of compounds **12** and **13**, to produce the protected fluoroglycine esters **21** and **22**, respectively.

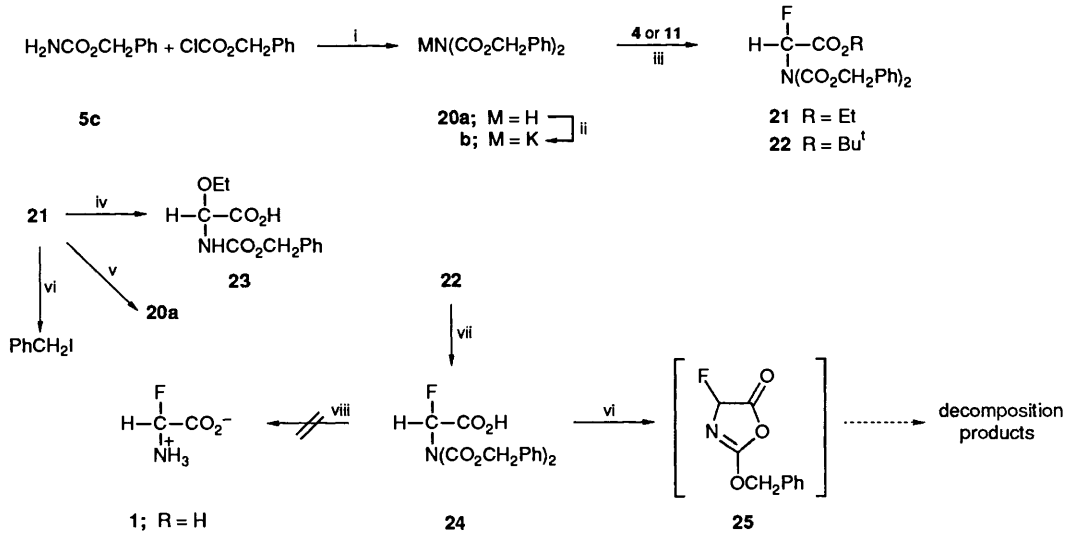
In contrast to the case of the t-butyl carbamate derivative **12**, attempted hydrolysis of the benzyl carbamate ethyl ester **21** produced unwanted products. Thus, saponification of compound **21** with aq. NaOH–EtOH gave the fluorination product **23**,§ presumably *via* the same mechanism as the formation of compound **15**. More gentle saponification conditions using LiOH or $Ba(OH)_2$ afforded the carbamate **20a**. Application of trimethylsilyl iodide (TMSI)[15] or other non-saponificative conditions[16] to compound **21** was also unsuccessful, yielding

* As the signals of **16** decreased in intensity, new signals which originated from compound **17** [δ_H 1.51 (9 H, s, But) and 6.27 (1 H, d, *J* 47.9 Hz); δ_F −157.06 (d, *J* 47.8 Hz)] and But F [δ_H 1.38 (9 H, d, *J* 21.2 Hz, But); δ_F −131.11 (10-plet, *J* 21.4 Hz)] appeared as monitored by NMR spectroscopy.

† Finally, a t-butyl signal [δ_H 1.28 (s)] which seemed to correspond to structure **18** was observed, and after removal of all volatile material no fluorine-containing compounds were found in the residue as checked by the NMR spectra.

‡ The yield of **20a** was sometimes meagre both because of its instability and the difficulty of separating it from the reaction admixture.

§ When the saponification of ester **21** was carried out with aq. NaOH–THF, *N*-benzyloxycarbonyl-α-hydroxyglycine was obtained.



Scheme 4 *Reagents and conditions:* i, KH, THF (64% yield); ii, aq. KOH, EtOH (100% yield); iii, DMF, 90–120 °C, 2–5 h (38–52% yield); iv, 5% NaOH, EtOH; v, LiOH or $Ba(OH)_2$, aq. THF; vi, TMSI, $CDCl_3$; vii, CF_3CO_2D, $CDCl_3$ (49% yield); viii, H_2/Pd-C, EtOH

mainly $PhCH_2I$ rather than EtI[21] and the decomposed counterpart. We finally tried the t-butyl ester **22**, treatment of which with CF_3CO_2D in $CDCl_3$ successfully produced the desired carboxylic acid **24** in 49% yield. Compound **24** was submitted to Pd/C-catalysed hydrogenation. We hoped that, after completion of the reaction, removal of the catalyst and evaporation of any volatile material would yield the target compound (**1**; R = H) in an almost pure state. Hydrogenolysis of an ethanolic solution of compound **24** in the presence of 5% Pd/C, however, to our extreme disappointment, produced again unidentified defluorination products, as verified by ^1H and ^{19}F NMR spectroscopy.* The use of TMSI for carbamate cleavage[21] of compound **24** was also attempted, but afforded initially the oxazolone **25**, which decomposed slowly, accompanied by defluorination as had already been observed (Scheme 4).

To sum up, we have developed the new amino functionality **20b** and have succeeded for the first time in the preparation of several novel α-fluorinated α-amino acid derivatives, viz. **12**, **13**, **16**, **21**, **22** and **24**. Although interconversion of protected amino acid **16** or **24** into the α-fluoro-α-amino acid itself was unsuccessful, we are currently examining the possible construction of the structural moiety of peptides containing an α-fluoro amino acid as a constituent.

Experimental

M.p.s were determined on a Yanagimoto apparatus and are uncorrected. B.p.s for micro-scale distillation indicate bath temperature. IR spectra were recorded on a JASCO A-102 or a Perkin-Elmer 1600 spectrometer. ^1H NMR spectra were measured in $CDCl_3$ with Me_4Si as internal standard and were recorded on a JEOL PMX-60 (60 MHz) or a JEOL GX-270 (270 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. Electron-impact (EI) mass spectra were taken with a JEOL JMS-300 spectrometer. Column chromatography was performed using Kieselgel 60 (Merck, Art. 9385).

* After substrate **24** had disappeared as monitored by TLC (*ca.* 30 h hydrogenation), the catalyst and the volatile materials were removed to give a semi-solid. Although debenzylation proceeded completely [NMR spectra (in CD_3COCD_3)], the characteristic signals [δ_H 4.92 (d, *J* 116.0 Hz); δ_F −150.81 (s) and −150.52 (d, *J* 115.8 Hz)] were difficult to assign to the target structure (**1**; R = H).

General Procedure for Preparation of Bromofluoroacetamide **6**.[12]—To a stirred, ice-cooled solution of trifluoroacetamide **5b** or benzyl carbamate **5c** (2 mmol) and an appropriate base (2 mmol) in tetrahydrofuran (THF) (10 cm^3) was added a solution of ethyl bromofluoroacetate **4** (370 mg, 2 mmol) in THF (2 cm^3). Precipitates formed immediately. The reaction mixture was stirred at 0–20 °C for 3.5–12 h. Evaporation of the solvent gave a semi-solid, which was chromatographed on silica gel with PhH–AcOEt (2:1) as eluent to afford the title compound **6** as crystals in 35–81% yield; m.p. 40.5–41.0 °C; ν_{max}(KBr)/cm^{-1} 3400 (NH) and 1685 (CO); δ_H(60 MHz) 6.65 (1 H, d, *J* 51.2 Hz, CHF) and 6.80 (2 H, br, NH_2); *m/z* 157,155 (M^+) and 113,111 ($M^+ - CONH_2$). Reaction of bromo ester **4** with ethanolic ammonia also produced the amide **6**.[12]

Ethyl 2-Hydroxy-2-(phenylacetamido)acetate **7**.—A mixture of phenylacetamide **5d** (203 mg, 1.5 mmol), bromo ester **4** (279 mg, 1.5 mmol) and Et_3N (152 mg, 1.5 mmol) in THF (6 cm^3) was heated at reflux for 2 days. The solvent was evaporated off under reduced pressure and the residue was chromatographed on silica gel with AcOEt–hexane (3:2) as eluent to afford the *title compound* **7** as crystals (180 mg, 50.6%). Recrystallization from AcOEt gave prisms, m.p. 122.0–122.5 °C (Found: C, 60.5; H, 6.2; N, 6.0. $C_{12}H_{15}NO_4$ requires C, 60.8; H, 6.4; N, 5.9%); ν_{max}(KBr)/cm^{-1} 3410 (OH), 3320 (NH), 1725 (CO_2), 1640 (CONH) and 1595 (Ph); δ_H(60 MHz) 1.26 (3 H, t, *J* 7.2 Hz, Me), 1.63 (1 H, br s, OH), 3.72 (2 H, s, CH_2CO), 4.27 (2 H, q, *J* 7.2 Hz, CH_2O), 5.92 (1 H, d, *J* 8.8 Hz, CH), 6.86 (1 H, br d, *J* 8.8 Hz, NH) and 7.40 (5 H, s, Ph); *m/z* 237 (M^+), 219 ($M^+ - H_2O$) and 164 ($M^+ - CO_2Et$).

General Procedure for the Preparation of Protected Amino Esters **11–13**.—A suspension of potassium salt **10a** or **10c** (4 mmol) in dry DMF (30 cm^3) was heated at 80 °C for 30 min. To the mixture was added dropwise a solution of bromo ester **4** or **9** (2 mmol) in dry DMF (10 cm^3) and the resultant solution was stirred at 90–120 °C for 2–5 h. The solvent was evaporated off under reduced pressure. Water (10 cm^3) was added to the residue and the whole was extracted with AcOEt (10 cm^3 × 3). The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a yellow oil, which was chromatographed on silica gel with PhH–AcOEt (3:1) or hexane–AcOEt (5:1) as eluent to afford the title compounds **11**,[6] **12** and **13**.

N,N-Bis(t-butoxycarbonyl)-α-fluoroglycine ethyl ester **12**. Obtained as *needles* (928 mg, 72.3%); m.p. 53.0 °C (Found: C,

52.3; H, 7.7; N, 4.6. $C_{14}H_{24}FNO_6$ requires C, 52.3; H, 7.5; N, 4.4%); ν_{max}(KBr)/cm^{-1} 2990 (CH) and 1780, 1763 and 1727 (CO); δ_H(270 MHz) 1.36 (3 H, t, *J* 7.1 Hz, CH_2*Me*), 1.55 (18 H, s, Bu^t × 2), 4.36 (2 H, q, *J* 7.1 Hz, CH_2) and 6.47 (1 H, d, *J* 48.6 Hz, CH); δ_F −156.78 (d, *J* 47.7 Hz); *m/z* 322 (M^+ + 1), 266 (M^+ − CH_2=CMe_2 + 1) and 57 (t-Bu$^+$).

N,N-*Bis*(*t-butoxycarbonyl*)-α-*fluoroglycine t-butyl ester* **13**. Obtained as an *oil* (1.05 g, 75.4%); b.p. 120–125 °C/4 × 10^{-3} mmHg (Found: C, 55.1; H, 8.2; N, 4.25. $C_{16}H_{28}FNO_6$ requires C, 55.0; H, 8.1; N, 4.0%); ν_{max}(film)/cm^{-1} 3050 (CH) and 1785, 1760 and 1725 (CO); δ_H(270 MHz) 1.51 (9 H, s, $CFCO_2Bu^t$), 1.53 (18 H, s, NCO_2Bu^t × 2) and 6.27 (1 H, d, *J* 47.9 Hz, CH); δ_F −157.04 (d, *J* 47.8 Hz); *m/z* 350 (M^+ + 1), 294 (M^+ − CH_2=CMe_2 + 1) and 57 (t-Bu$^+$).

Also prepared was:

N-(*t-Butoxycarbonyl*)-α-*ethoxyglycine ethyl ester* **15**. Obtained as prisms; m.p. 176.5–177.0 °C; ν_{max}(KBr)/cm^{-1} 3380 and 3330 (NH), 2960 (CH), 1742 ($CHCO_2$) and 1687 ($NHCO_2$); δ_H(60 MHz) 1.21 (3 H, t, *J* 7.1 Hz, $CHOCH_2$*Me*), 1.24 (3 H, t, *J* 7.1 Hz, CO_2CH_2*Me*), 1.48 (9 H, s, Bu^t), 3.72 (2 H, q, *J* 7.1 Hz, $CHOCH_2$), 4.27 (2 H, q, *J* 7.1 Hz, CO_2CH_2), 5.32 (1 H, d, *J* 11.4 Hz, CH) and 5.70 (br d, *J* 11.4 Hz, NH); *m/z* 248 (M^+ + 1), 202 (M^+ − OEt) and 102 (CO_2Bu^t).

N,N-*Bis*(*t-butoxycarbonyl*)-α-*fluoroglycine* **16**.—A mixture of the ester **12** (102 mg, 0.32 mmol) in 5% NaOH (0.5 cm^3)–EtOH (0.5 cm^3) was stirred at room temperature for six hours. The mixture was evaporated and diethyl ether (5 cm^3) was added to the residue. The mixture was extracted with 10% Na_2CO_3 (5 cm^3 × 3). The aq. layer was acidified with 5% HCl and extracted with $CHCl_3$ (5 cm^3 × 3). The extract was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave the *title compound* **16** as a viscous oil (86 mg, 92.4%) [Found: *m/z* 222.039. $C_7H_9FNO_6$ (M^+ − CH_2=CMe_2 − Me) requires *m/z* 222.041. Found: *m/z* 193.075. $C_7H_{12}FNO_4$ (M^+ − CH_2=CMe_2 − CO_2) requires *m/z* 193.075. Found: *m/z* 174.077. $C_7H_{12}NO_4$ (M^+ − CH_2=CMe_2 − CO_2 − F) requires *m/z* 174.077]; ν_{max}(film)/cm^{-1} 3380 (OH) and 1705 (CO); δ_H(270 MHz) 1.53 (18 H, s, Bu^t × 2), 5.45 (1 H, br s, OH) and 6.47 (1 H, d, *J* 47.6 Hz, CHF); δ_F −156.31 (d, *J* 47.8 Hz); *m/z* 222 (M^+ − CH_2=CMe_2 − Me), 193 (M^+ − CH_2–CMe_2 − CO_2), 174 (M^+ − CH_2=CMe_2 − CO_2 − F) and 57 (t-Bu$^+$).

Dibenzyl Iminodicarboxylate **20a**.—To a solution of benzyl carbamate **5c** (1.76 g, 11.6 mmol) in dry THF (30 cm^3) at 0 °C was added potassium hydride (24.6% suspension in mineral oil; 2.10 g, 12.9 mmol) and the mixture was stirred for 30 min. A solution of benzyl chloroformate (2.39 g, 13.9 mmol) in dry THF (3 cm^3) was added and the mixture was stirred at room temperature for 20 min. The mixture was evaporated and water (10 cm^3) was added to the residue. The aq. solution was acidified with 10% HCl and then extracted with AcOEt (30 cm^3 × 3). The extract was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave an oil, which was dissolved in diethyl ether (40 cm^3). Sodium hydride (60% dispersion in mineral oil) was added in portions to the solution until no more gas generation was observed. After storage at room temperature for 1 h, crystals (sodium salt) were collected on a filter. The crystals were dissolved in water (20 cm^3), the solution was acidified with 10% HCl and extracted with AcOEt (20 cm^3 × 3), and the extract was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a residual oil, which was dissolved in CCl_4. The resultant solution was partially concentrated to give the *title compound* **20a** as crystals (2.11 g, 63.8%). An analytical sample was obtained by recrystallization from CCl_4 as needles, m.p. 110.5–111.0 °C (Found: C, 67.6; H, 5.25; N, 5.1. $C_{16}H_{15}NO_4$ requires C, 67.35; H, 5.3; N, 4.9%); ν_{max}(KBr)/cm^{-1} 3200 (NH) and 1770 (CO); δ_H(270 MHz) 1.62 (1 H, br s, NH), 5.22 (4 H, s, CH_2 × 2) and 7.35 (10 H, s, Ph × 2); *m/z* 285 (M^+), 194 (M^+ − CH_2Ph), 177 (M^+ − OCH_2Ph) and 91 ($PhCH_2^+$).

Dibenzyl Iminodicarboxylate Potassium Salt **20b**.—To a solution of dibenzyl iminodicarboxylate **20a** (1.56 g, 5.5 mmol) in EtOH (6 cm^3) was added slowly a solution of KOH (377 mg, 6.7 mmol) in water (2 cm^3). The solvent was evaporated off and residual crystals were dried over P_2O_5 under reduced pressure for two days. The title compound **20b** was obtained as crystals in quantitative yield (1.75 g); m.p. 270 °C; ν_{max}(KBr)/cm^{-1} 1695 (CO) and 1610 (Ph).

General Procedure for Preparation of Triesters **21** *and* **22**.—Compounds **21** and **22** were prepared by reaction of bromo esters **4** and **9** with the salt **20b** in hot DMF by a procedure similar to that of the preparation of triesters **12** and **13**.

N,N-*Bis*(*benzyloxycarbonyl*)-α-*fluoroglycine ethyl ester* **21**. Obtained as an *oil* in 51.5% yield; b.p. 175–185 °C/4 × 10^{-3} mmHg [Found: C, 61.7; H, 5.05; N, 3.7%; *m/z* 298.066. $C_{20}H_{20}FNO_6$ requires C, 61.7; H, 5.2; N, 3.6%; $C_{13}H_{13}FNO_6$ (M^+ − CH_2Ph) requires *m/z* 298.066]; ν_{max}(film)/cm^{-1} 3000 (CH) and 1775, 1755 and 1720 (CO); δ_H(270 MHz) 1.15 (3 H, t, *J* 7.2 Hz, Me), 4.06 (2 H, q, *J* 7.2 Hz, C*H*$_2$Me), 5.28 (4 H, AB-type q, Δδ 0.04 ppm, *J* 12.0 Hz, C*H*$_2$Ph × 2), 6.53 (1 H, d, *J* 47.4 Hz, CH) and 7.34 (10 H, s, Ph × 2); δ_F −157.59 (d, *J* 46.0 Hz); *m/z* 390 (M^+ + 1), 298 (M^+ − CH_2Ph) and 91 ($PhCH_2^+$).

N,N-*Bis*(*benzyloxycarbonyl*)-α-*fluoroglycine t-butyl ester* **22**. Obtained as an *oil* in 37.6% yield; b.p. 190–195 °C/6 × 10^{-3} mmHg [Found: C, 63.7; H, 5.6; N, 3.2%; *m/z* 361.098. $C_{22}H_{24}FNO_6$ requires C, 63.3; H, 5.8; N, 3.4%; $C_{18}H_{16}FNO_6$ (M^+ − CH_2=CMe_2) requires *m/z* 361.096]; ν_{max}(film)/cm^{-1} 3000 (CH) and 1770, 1740 and 1725 (CO); δ_H(270 MHz) 1.39 (9 H, s, Bu^t), 5.27 (4 H, AB-type q, Δδ 0.05 ppm, *J* 12.2 Hz, CH_2 × 2), 6.41 (1 H, d, *J* 47.4 Hz, CH) and 7.33 (10 H, s, Ph × 2); δ_F −157.29 (d, *J* 47.8 Hz); *m/z* 417 (M^+), 361 (M^+ − CH_2=CMe_2) and 91 ($PhCH_2^+$).

Also prepared was *N*-(benzyloxycarbonyl)-α-ethoxyglycine **23**. Obtained as prisms; m.p. 183.0–184.5 °C; ν_{max}(KBr)/cm^{-1} 3350 (NH) and 1760 and 1660 (CO_2); δ_H(60 MHz) 1.25 (3 H, t, *J* 7.1 Hz, Me), 3.70 (2 H, q, *J* 7.1 Hz, C*H*$_2$Me), 5.17 (2 H, s, C*H*$_2$Ph), 5.41 (1 H, d, *J* 9.4 Hz, CH), 6.07 (1 H, br d, *J* 9.4 Hz, NH), 7.35 (5 H, s, Ph) and 8.77 (1 H, br s, OH); *m/z* 254 (M^+ + 1), 208 (M^+ − OEt) and 164 (M^+ − OEt − CO_2).

N,N-*Bis*(*benzyloxycarbonyl*)-α-*fluoroglycine* **24**.—To a solution of compound **22** (120 mg, 0.289 mmol) in $CDCl_3$ (0.5 cm^3) was added dropwise CF_3CO_2D until the starting material had disappeared as monitored by ^{1}H NMR spectroscopy. Evaporation of the solvent gave an oil, which was dissolved in diethyl ether (5 cm^3). The ethereal solution was extracted with 10% Na_2CO_3 (2 cm^3 × 3). The aq. layer was carefully acidified with 5% HCl and extracted with $CHCl_3$ (5 cm^3 × 3) and the extract was dried over $MgSO_4$. Evaporation of the solvent gave the *title compound* **24** as a viscous oil (51 mg, 48.9%) [Found: *m/z* 360.088. $C_{18}H_{15}FNO_6$ (M^+ − H) requires *m/z* 360.088]; ν_{max}(film)/cm^{-1} 3380 (OH) and 1710 (CO); δ_H(270 MHz) 5.27 (4 H, s, CH_2 × 2), 5.70 (1 H, br, OH), 6.56 (1 H, d, *J* 47.1 Hz, CHF) and 7.32 (10 H, s, Ph × 2); δ_F −157.41 (d, *J* 45.8 Hz); *m/z* 360 (M^+ − 1), 91 ($PhCH_2^+$) and 20 (HF).

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References

1 J. T. Welch, *Tetrahedron*, 1987, **43**, 3123; M. Schlosser, *Tetrahedron*, 1978, **34**, 3; A. Jordaan, *S. Afr. J. Sci.*, 1977, **73**, 201; J. T. Welch and S. Eswarakrishnan, *J. Chem. Soc., Chem. Commun.*, 1985, 186.

2 N. A. Thornberry, H. G. Bull, D. Taub, W. J. Greenlee, A. A. Patchett and E. H. Cordes, *J. Am. Chem. Soc.*, 1987, **109**, 7543; D. F. Loncrini and R. Filler, *Adv. Fluorine Chem.*, 1970, **6**, 43; T. Tsushima, K. Kawada, J. Nishikawa, T. Sato, K. Tori, T. Tsuji and S. Misaki, *J. Org. Chem.*, 1984, **49**, 1163; P. Bey, J. Vevert, V. V. Dorsselaer and M. Kolb, *J. Org. Chem.*, 1979, **44**, 2732; I. Ojima, K. Kato, K. Nakahashi, T. Fuchikami and M. Fujita, *J. Org. Chem.*, 1989, **54**, 4511; A. I. Ayi, M. Remli and R. Guedj, *Tetrahedron Lett.*, 1981, **22**, 1505; P. Bey and J. P. Vevert, *Tetrahedron Lett.*, 1978, 1215; L. Somekh and A. Shanzer, *J. Am. Chem. Soc.*, 1982, **104**, 5836.

3 K. Uchida and H. Tanaka, *Yuki Gosei Kagaku Kyokaishi*, 1988, **46**, 977 (*Chem. Abstr.*, 1989, **110**, 75997d).

4 P. Bey, F. Gerhart, V. V. Dorsselaer and C. Danzin, *J. Med. Chem.*, 1983, **26**, 1551; T. Tsushima, K. Kawada, T. Tsuji and K. Tawara, *J. Med. Chem.*, 1985, **28**, 253; R. B. Silverman and R. H. Abeles, *Biochemistry*, 1977, **16**, 5515.

5 R. Filler and Y. Kobayashi, *Biomedicinal Aspects of Fluorine Chemistry*, Kodansha, Tokyo, 1982; J. Mann, *Chem. Soc. Rev.*, 1987, **16**, 381.

6 Y. Takeuchi, M. Asahina, K. Nagata and T. Koizumi, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2203.

7 M. Hudlicky, *Chemistry of Organic Fluorine Compounds*, Ellis Horwood, Chichester, 1976.

8 E. W. Colvin, G. W. Kirby and A. C. Wilson, *Tetrahedron Lett.*, 1982, **23**, 3835; G. Boche, M. Bernheim and W. Schrott, *Tetrahedron Lett.*, 1982, **23**, 5399; P. Beak and B. J. Kokko, *J. Org. Chem.*, 1982, **47**, 2822; G. Gennari, L. Colombo and G. Bertolini, *J. Am. Chem. Soc.*, 1986, **108**, 6394; D. A. Evans, T. C. Britton, R. L. Dorow and J. F. Dellaria, *J. Am. Chem. Soc.*, 1986, **108**, 6395; L. A. Trimble and J. C. Vederas, *J. Am. Chem. Soc.*, 1986, **108**, 6397; W. Klötzer, H. Baldinger, E. M. Karpitschka and J. Knoflach, *Synthesis*, 1982, 592; Y. Tamura, J. Minamikawa and M. Ikeda, *Synthesis*, 1977, 1 and references cited therein.

9 R. D. Chambers, *Fluorine in Organic Chemistry*, Wiley, New York, 1973, p. 64; R. D. Chambers and M. R. Bryce, *Stud. Org. Chem. (Amsterdam)*, 1987, **5**, 271.

10 Y. Takeuchi, H. Ogura, Y. Ishii and T. Koizumi, *Chem. Pharm. Bull.*, 1990, **38**, 2404.

11 P. A. Harland and P. Hodge, *Synthesis*, 1984, 941.

12 M. H. Pendleburg, L. Phillips and V. Wray, *J. Chem. Soc., Perkin Trans. 2*, 1974, 787.

13 S. Gabriel, *Ber. Dtsch. Chem. Ges.*, 1887, **20**, 2224.

14 J. O. Osby, M. G. Martin and B. Ganem, *Tetrahedron Lett.*, 1984, **25**, 2093; S. Wolfe and S. K. Hasan, *Can. J. Chem.*, 1970, **48**, 3572; S. Kukolja and S. R. Lammert, *J. Am. Chem. Soc.*, 1975, **97**, 5582; T. Kamiya, M. Hashimoto, O. Nakaguchi and T. Oku, *Tetrahedron*, 1979, **35**, 323; S. K. Boyer, R. A. Pfund, R. E. Portmann, G. H. Sedelmeier and H. F. Wetter, *Helv. Chim. Acta*, 1988, **71**, 337.

15 T. Ho and G. A. Olah, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 774; M. E. Jung and M. A. Lyster, *J. Am. Chem. Soc.*, 1977, **99**, 968; G. A. Olah, S. C. Narang, B. B. Gupta and R. Malhotra, *J. Org. Chem.*, 1979, **44**, 1247; T. Morita, Y. Okamoto and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 1978, 874.

16 F. C. Chang and N. F. Wood, *Tetrahedron Lett.*, 1964, 2969; P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 1970, 4459; T. R. Kelly, H. M. Dali and W. Tsang, *Tetrahedron Lett.*, 1977, 3859; D. Liotta, U. Sunay, H. Santiesteban and W. Markiewicz, *J. Org. Chem.*, 1981, **46**, 2605.

17 C. T. Clarke, J. D. Elliott and J. H. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1088.

18 Y. Takeuchi, H. Ogura, Y. Ishii and T. Koizumi, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1721; J. D. Park, H. C. Cummings and J. R. Lacher, *J. Org. Chem.*, 1958, **23**, 1785.

19 Y. Takeuchi, M. Asahina, K. Hori and T. Koizumi, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1149.

20 L. Grehn and U. Ragnarsson, *Synthesis*, 1987, 275.

21 R. S. Lott, V. S. Chauhan and C. H. Stammer, *J. Chem. Soc., Chem. Commun.*, 1979, 495.

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