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THE SYNTHESIS OF A FLUORINATED ANALOGUE OF 5-AMINOLAEVULINIC ACID, A POTENTIAL INHIBITOR OF PORPHYRIN BIOSYNTHESIS

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SUMMARY

5-Amino-2-fluorolaevulinic acid **3** has been synthesized in high yield by modification of a new route to 5-aminolaevulinic acid (ALA), involving γ-lactone intermediates. Initial studies suggest that **3** is an inhibitor of ALA dehydratase, an early enzyme of tetrapyrrole biosynthesis.

INTRODUCTION

5-Aminolaevulinic acid (ALA) is the first universal intermediate in porphyrin biosynthesis. In plants and anaerobic bacteria it is synthesized from glutamate whereas in some other bacteria, fungi, and animals it is derived from glycine and succinyl CoA [1]. In all organisms two molecules of ALA **1** are condensed by the enzyme ALA dehydratase to give the pyrrole porphobilinogen **2** (Scheme 1). Four molecules of **2** then combine to give uroporphyrinogen III, the precursor of all natural tetrapyrroles.

Part of the mechanism for the condensation of two ALA molecules is essentially an aldol reaction between the two ketone groups and it necessarily involves the generation of an enolate or an equivalent such as an enamine. We reasoned that the mechanism could be diverted by the presence of a leaving group such as fluoride at C-2. Incubation of 2-fluoroALA **3** with ALA dehydratase could result in elimination of fluoride to give a species such as **4** at the active

Scheme 1.

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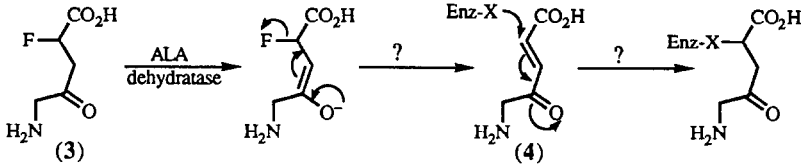


Scheme 2.

site which would be a good Michael acceptor and might cause irreversible alkylation of a nucleophilic residue on the enzyme (Scheme 2).

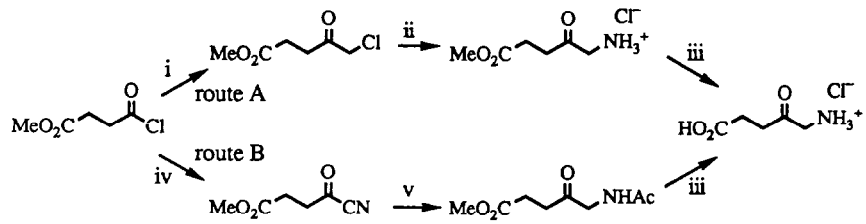
The choice of the fluorine substituent in the putative inhibitor **3** is determined not only by its leaving group ability but also its small size which means that it is unlikely to experience large steric interactions at the active site. Fluorinated substrate analogues have frequently been found to be irreversible or competitive inhibitors of enzymes [2].

In this paper we present our approaches to the synthesis of 2-fluoroALA **3** including the ultimately successful one which was based on a new route to ALA itself.

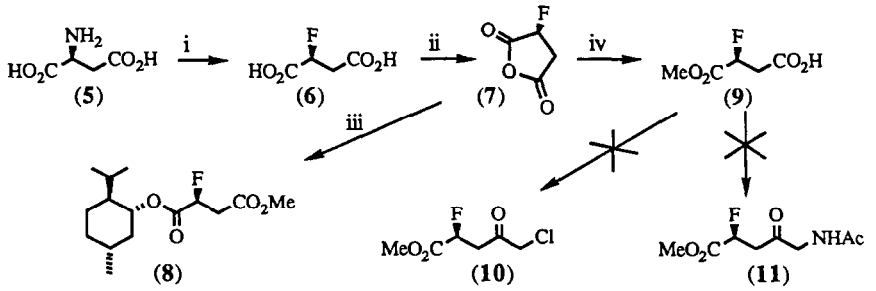
RESULTS

Many syntheses of ALA have been developed since its biological significance was first realized [3-10] and a number of these methods have been used for the synthesis of isotopically labelled forms of ALA [11-18]. Two of the most direct routes start with monomethyl succinate. They are Gutman's modification [15] of the syntheses of Neuberger and Scott [3] and Shemin *et al.* [4] (route A) and the method of Pfaltz and Anwar [10] (route B, Scheme 3).

These seemed appropriate routes for the synthesis of 2-fluoroALA, especially as fluorosuccinic acid is readily obtained by the diazotization of aspartic acid in HF/pyridine [19]. Furthermore this approach offered the prospect of stereospecifically fluorinated products if optically active aspartic acid is used. To confirm that the diazotization reaction (expected to



Scheme 3. *Reagents:* i, CH_2N_2 then HCl; ii, NaN_3 then H_2/Pd; iii, HCl; iv, CuCN; v, Zn/AcOH/Ac_2O.

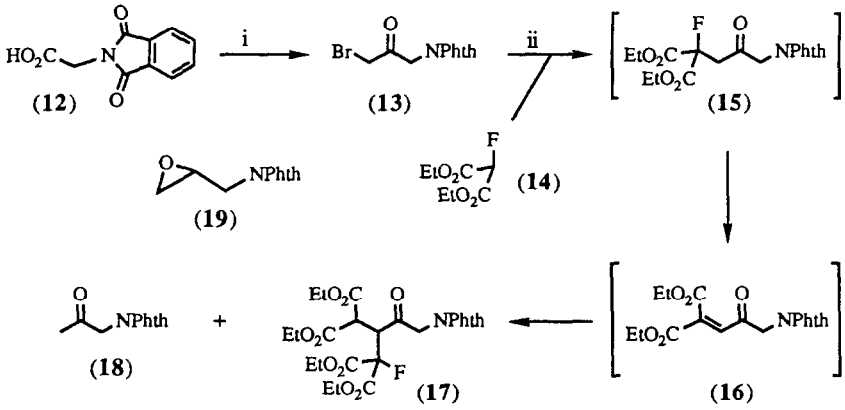


Scheme 4. *Reagents:* i, $NaNO_2$/HF/Pyr; ii, TFAA; iii, menthol/DMAP then CH_2N_2; iv, MeOH.

proceed with overall retention of configuration) is stereospecific, the fluorosuccinic acid **6** derived from aspartic acid **5** was converted into a chiral ester by cyclization to the anhydride **7** using trifluoroacetic anhydride and then treatment with (+)-menthol and dimethylaminopyridine (Scheme 4). Attack of the nucleophile occurs exclusively at the more activated carbonyl adjacent to the fluorine. The resulting monoacid was methylated with diazomethane to give 1-menthyl 4-methyl 2-fluorosuccinate **8**. In this compound the ^1H n.m.r. spectrum showed two sets of signals for the two diastereoisomers when starting with racemic aspartic acid. Better separation was observed, however in the ^1H decoupled ^{19}F n.m.r. spectrum, which showed two singlets separated by 0.26 p.p.m. When starting from (*S*)-aspartic acid the ratio of the two sets of signals was 92 : 8 in favour of the more upfield signal, showing that the diazotization reaction is largely stereospecific. The small amount of the minor diastereoisomer may indicate a small loss of stereospecificity but it could also be explained by either of the starting materials, aspartic acid or menthol, being less than 100% optically pure – this was not investigated further.

The anhydride **7** was treated with methanol to give specifically the 1-methyl ester **9**. Unfortunately all attempts to follow either route A or B starting with **9** to give the chloromethyl ketone **10** or the acetamidomethyl ketone **11** were unsuccessful. We suppose that either elimination of HF was occurring or the electronegativity of the fluorine was activating the carbonyl groups, producing unwanted side-reactions.

Our next approach to 2-fluoroALA was to adapt another synthesis of ALA, which has been used several times [5,7,16], involving alkylation of a malonate diester with the bromoketone **13** derived from phthaloylglycine **12** [5] (Scheme 5). It was envisaged that the use of commercially available diethyl fluoromalonate would yield **15** and thence 2-fluoroALA upon acidic hydrolysis. In the event, reaction of the sodium salt of fluoromalonate **14** with bromoketone **13** gave not the desired adduct **15** but a diadduct **17** which arises by elimination of HF from **15** followed by Michael addition of a second malonate anion to the resulting alkene



Scheme 5. *Reagents:* i, $ClCO_2Et/Et_3N$ then CH_2N_2 then HBr; ii, (**14**)/NaH/DMF.

16. Surprisingly the methyl ketone **18** was also isolated. Under no conditions was any of the desired product **15** isolated.

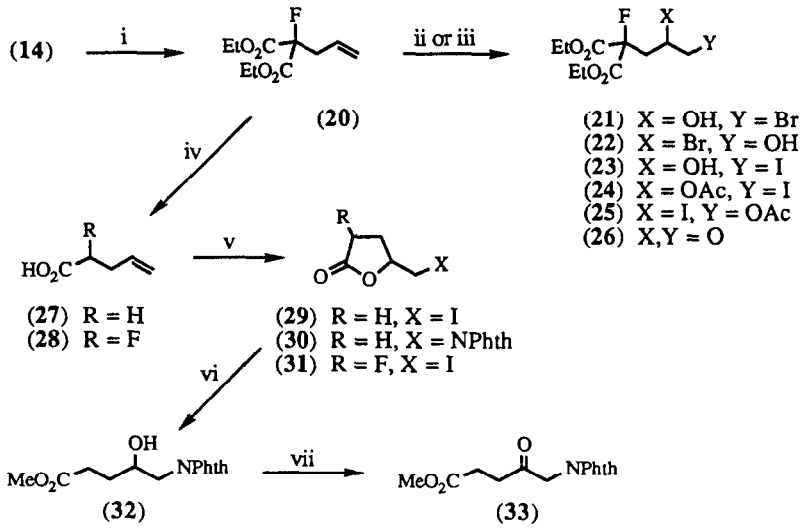
In order to avoid the elimination of HF, facilitated by the ketone group, alkylation of the fluoromalonate **14** with phthalimido-epoxide **19** [20] was attempted but no reaction between these two components was observed. Clearly one problem is that the electronegative fluorine atom reduces the reactivity of the malonate anion.

Reaction of the anion of fluoromalonate **14** with more reactive alkylating agents is successful, however, and allylation with allyl bromide is known [21] to give the allylfluoromalonate **20** (Scheme 6). A suitably selective difunctionalization of the double bond of **20** could lead to a synthesis of 2-fluoroALA and this was the next approach to be explored.

The first attempted reaction was bromohydrin formation using N-bromosuccinimide in moist DMSO [22], which was expected to result in Markovnikov addition giving the secondary alcohol **21**. In the event this was the minor product with the major product (2:1) being the isomeric primary alcohol **22**. Presumably the combined electron-withdrawing effects of the fluorine atom and the two ester groups reduce the partial positive charge at the secondary carbon atom of the bromonium ion and thus reduce the amount of nucleophilic attack at this site. No way was found to separate the two isomers.

Similarly reaction of the alkene **20** with silver acetate and iodine [23] also gave a mixture of products containing iodohydrin **23**, both iodo-acetates **24** and **25** and epoxide **26**. As straightforward addition reactions of the alkene were not providing the required degree of specificity, we turned to methods that involved lactonization to provide the regiospecificity.

Iodolactonization of γ,δ-unsaturated acids such as pent-4-enoic acid **27** are known to yield the five-membered lactone **29** rather than the corresponding six-membered lactone [24]. In order to show that this could lead to a synthesis of ALA, the unfluorinated iodolactone **29**



Scheme 6. *Reagents:* i, NaH/allyl bromide/DMF; ii, NBS/DMSO/H_2O; iii, AgOAc/I_2; iv, NaCl/DMSO/H_2O then KOH; v, I_2/$NaHCO_3$ then PhthNK/DMF; vi, KOH then CH_2N_2; vii, CrO_3/H_2SO_4.

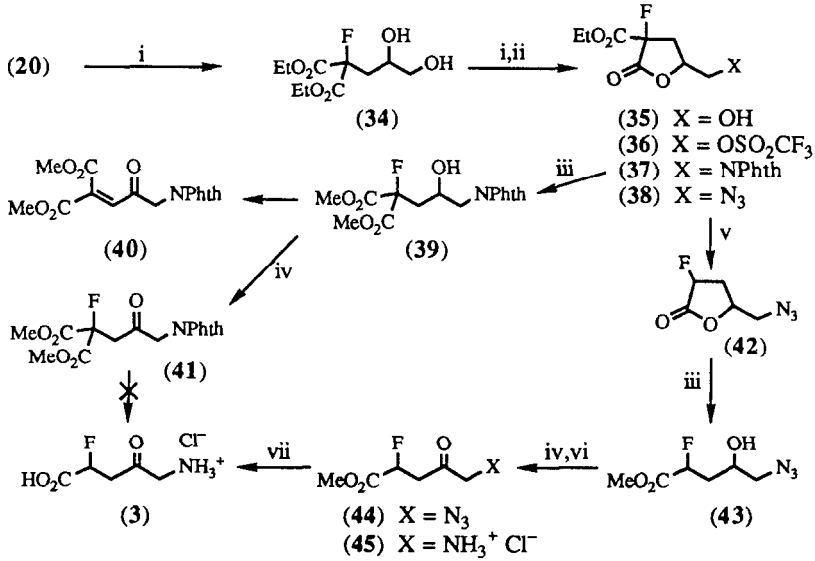
was reacted with potassium phthalimide, the resulting lactone **30** was opened to the hydroxy ester **32** with potassium hydroxide followed by diazomethane, and Jones oxidation gave the protected ALA derivative **33** in 50% overall yield from the pentenoic acid **27**. Deprotection of the phthalimidoester **33** has already been reported [3,25]. And so this sequence of reactions represents a new high-yield synthesis of ALA **1** from a readily available, inexpensive starting material.

Applying this synthesis of ALA to the synthesis of 2-fluoroALA did not prove so simple. The fluoromalonate **20** was cleanly decarboethoxylated using NaCl in moist DMSO (Krapcho conditions [26]) and the resulting 2-fluoropent-4-enoate ester was hydrolysed to the acid **28**. However, iodolactonization using the previous conditions only gave a very small yield of the required product **31** and various modifications of the conditions did not improve the yield beyond 16%. It was thought that the electronegativity of the fluorine atom causes the lactone to be rapidly hydrolysed in the basic conditions used in the reaction.

As an alternative route to a 5-membered lactone, the alkene **20** was dihydroxylated with a catalytic amount of osmium tetroxide regenerated with N-methylmorpholine-N-oxide. This, in fact, gave only a small amount of the diol **34** as the majority cyclized *in situ* to the required lactone **35** (Scheme 7). Conversion of the alcohol into the phthalimide **37** was first attempted using phthalimide, triphenylphosphine, and diethyl azodicarboxylate (Mitsunobu conditions

[27]) but no reaction was observed. Instead **37** was made by conversion of the alcohol **35** into its triflate **36** followed by reaction with potassium phthalimide. Hydrolysis of the lactone and re-esterification with diazomethane gave the ring-opened dimethyl ester **39**. Jones oxidation of **39** using the previous conditions resulted in the formation of approximately equal amounts of the elimination product **40** and the desired fluoro compound **41** but, using a modified work-up procedure, the elimination was avoided and solely **41** was obtained in high yield. Unfortunately the final step, deprotection and decarboxylation, requires strongly acidic conditions for the hydrolysis of the phthalimide. While this is successful for similar derivatives of unfluorinated ALA [16], the fluorinated compound **41** did not survive these conditions.

In order to overcome the problems in the deprotection of **41**, two modifications to the route were made. First, azide was used as a protected form of amine, in place of phthalimide, as the deprotection involves a much milder hydrogenation step. Second, the decarboxylation was performed earlier using Krapcho's conditions [26]. Thus treatment of the triflate **36** with sodium azide gave **38** and decarboethoxylation gave lactone **42**. Hydrolysis, esterification, and oxidation as before gave the azidoketone **44** *via* alcohol **43**. Hydrogenation over palladium-on-charcoal revealed the amine, which was kept protonated as its hydrochloride **45**. Finally mild acidic hydrolysis of the ester cleanly gave 2-fluoroALA **3** as its hydrochloride. All the yields in



Scheme 7. *Reagents:* i, OsO_4/NMO; ii, Tf_2O/Pyr then PhthNK or NaN_3; iii, KOH then CH_2N_2; iv, CrO_3/H_2SO_4; v, NaCl/DMSO/H_2O; vi, H_2/Pd; vii, aq. HCl.

this synthesis were satisfactory and the overall yield for the 9 steps from diethyl fluoromalonate and allyl bromide was 11%.

Only preliminary studies of the effect of 2-fluoroALA **3** on the enzyme ALA dehydratase have been undertaken so far [28]. Using an enzyme preparation from the unicellular alga *Euglena gracilis*, **3** showed significant inhibition at concentrations of 0.5–2 mM (approximately equal to the K_M for ALA for this enzyme) but did not show activity as a substrate or as an irreversible inhibitor.

CONCLUSIONS

The synthesis of 2-fluoroALA **3** described above is reasonably short and high-yielding and could perhaps be further optimized. The 2-fluoroALA inhibits ALA dehydratase from *Euglena gracilis*. ALA dehydratase is an important enzyme for plants and algae which make chlorophylls and inhibition of this enzyme could lead to an effective herbicide (assuming an inhibitor can be found that does not also inhibit the biosynthesis of porphyrins in mammals).

Furthermore if 2-fluoroALA acts as a poor substrate for one of the halves of the porphobilinogen product then not only will this step be slowed but also a fluoroPBG will be formed as a product and this may inhibit the next step in the pathway. Indeed we have recently found [29] that PBG having a fluorine substituent α to the carboxyl of the propionate side chain is a very effective inhibitor of PBG deaminase as well as itself being a poor substrate.

This type of behaviour of fluorinated substrates, not unexpected of compounds which so closely resemble the natural substrate, means that they have more opportunities to disrupt an extended biosynthetic pathway such as that of the chlorophylls and are therefore well worth investigating.

EXPERIMENTAL

^1H and ^{13}C chemical shifts are quoted relative to tetramethylsilane at $\delta = 0$ ppm and ^{19}F chemical shifts are relative to external trifluoroacetic acid at $\delta = 0$ ppm.

(*S*)-2-Fluorosuccinic anhydride **7**

(*S*)-2-Fluorosuccinic acid (27 mg, 0.23 mmol) (prepared as in ref. 18) was stirred in trifluoroacetic anhydride (2 ml) at 0 °C under argon. After 3 h excess solvents were evaporated under reduced pressure at 0 °C to yield the crude anhydride **7** (25 mg, 86%), which was used directly in subsequent reactions (Found: 119.0140. $C_4H_4O_3F$ (M^++H) requires 119.0144); ν_{max} (thin film) 1 800 (C=O) cm^{-1}; δ_H (400 MHz, CD_3COCD_3) 3.23 (1 H, dd, *J* 24.5, 19, and 5.5 Hz, CH_AH_B), 3.44 (1 H, dd, *J* 19, 12.5 and 8.5 Hz, CH_AH_B) and 5.55 (1 H, ddd, *J* 50.5, 8.5, and 5.5 Hz, CHF); δ_F (235 MHz, $CDCl_3$) −114.7 (ddd, *J* 50.5, 24.5, and 12.5 Hz); *m/z* (EI) 119 (M^++H, 58%), 113 (10), 102 (25), 99 (96) and 85 (40).

1-(+)-Menthyl 4-methyl (*S*)-2-fluorosuccinate **8**

(*S*)-2-Fluorosuccinic anhydride from diacid **6** (21 mg) was stirred with dry CH_2Cl_2 (1 ml), (+)-menthol (30 mg, 0.19 mmol), and 4-(dimethylamino)pyridine (4 mg) at room temperature for 20 h, then at 40 °C for 24 h. Dichloromethane was added and the mixture was extracted with sat. aq. $NaHCO_3$. The acidified aqueous layers were extracted with EtOAc and the extracts were dried, evaporated, and treated with excess ethereal diazomethane. Chromatography on silica, using hexane/diethyl ether (4:1) (R_f 0.27) gave the diester **8** as an oil (5 mg, 10% from diacid); δ_H (250 MHz, $CDCl_3$) 0.76 (3 H, d, *J* 7 Hz, ring CH_3), 0.89 and 0.90 (each 3 H, dd, *J* 7 Hz, isopropyl CH_3), 0.9–2.05 (8 H, m, menthyl-**H**), 2.925 and 2.935 (each 1 H, dd, *J* 23 and 7 and *J* 25 and 5 resp., CH_2CHF), 3.73 (3 H, s, CH_3O), 4.80 (1 H, tdd, *J* 11, 6, and 4 Hz, CHO_2C) and 5.27 (1 H, ddd, *J* 47, 7, and 5 Hz, CHF); δ_F (235 MHz, CD_3COCD_3) –114.58 (dt, *J* 48.2 and 23.8 Hz); *m/z* (FD) 288 (100%).

The same procedure starting with racemic 2-fluorosuccinic acid gave a mixture of the above diester **8** and its diastereoisomer (ratio 42:58), which were not separated. For the diastereoisomer: δ_H (250 MHz, $CDCl_3$) 0.75 (3 H, d, *J* 7 Hz, ring CH_3), 0.89 and 0.90 (each 3 H, d, *J* 7 Hz, isopropyl CH_3), 0.96–2.05 (8 H, m, menthyl-**H**), 2.87-3.00 (2 H, m, CH_2CHF), 3.73 (3 H, s, CH_3O), 4.79 (1 H, m, CHO_2C), and 5.25 (1 H, ddd, *J* 47 Hz, 6.5, and 5 Hz, CHF); δ_F (235 MHz, CD_3COCD_3) –114.32 (dt, *J* 47 and 25 Hz); *m/z* (FD) 288 (100%).

1-Methyl (*S*)-2-fluorosuccinate **9**

The anhydride **7** (25 mg, 0.21 mmol) was dissolved in dry MeOH (5 ml) and stirred at room temperature for 3.5 h. Evaporation and chromatography, eluting with $CHCl_3$/acetone/formic acid (16:3:1), gave the monoester **9** as an oil (21 mg, 70%) (Found: 132.0217. $C_5H_5O_3F$ (M^+–H_2O) requires 132.0223); ν_{max} (thin film) 3 300–2 600 (OH) and 1 740 (C=O) cm^{-1}; δ_H (400 MHz, CD_3COCD_3) 2.91–3.03 (2 H, m, CH_2), 3.77 (3 H, s, CH_3O), 5.35 (1 H, ddd, *J* 47, 7, and 4 Hz, CHF), and 10.20 (1 H, br s, OH); δ_C (100 MHz, CD_3COCD_3) 37.5 (d, *J* 22 Hz, CH_2), 52.6 (CH_3O), 86.3 (d, *J* 183 Hz, CHF), 169.6 (d, *J* 22 Hz, CHFCO), and 170.3 (CH_2CO); δ_F (235 MHz, CD_3COCD_3) –114.9 (ddd, *J* 47, 26, and 24 Hz); *m/z* (EI) 132 (M^+–H_2O, 5%), 128 (12), 119 (M^+–CH_3O, 24), 102 (13), 99 (23), and 85 (13).

Tetraethyl 1-Fluoro-2-(2-phthalimidoacetyl)propane-1,1,3,3-tetracarboxylate **17**

Diethyl fluoromalonate (178 mg, 1.0 mmol) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in oil; 40 mg, 1.0 mmol) in dry DMF (5 ml) under argon. After 1 h, a solution of the bromoketone **13** (238 mg, 0.85 mmol) in dry DMF (1 ml) was added. After 16 h the majority of the solvent was evaporated. Water was added and the mixture was extracted with CH_2Cl_2. Chromatography, eluting with ether (10–60%) in hexane,

gave (in order of elution) recovered bromoketone **13** (50 mg), 1-phthalimidopropanone (**18**) as needles (20 mg, 12%), m.p. 104–107 °C (from diethyl ether) (Found: 203.0597. $C_{11}H_9NO_3$ requires 203.0597); ν_{max} (CH_2Cl_2) 1 720 (C=O) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 2.26 (3 H, s, $COCH_3$), 4.49 (2 H, s, CH_2N), and 7.74 and 7.86 (each 2 H, dd, *J* 5.5 and 3 Hz, Ar**H**); *m/z* (EI) 203 (M^+, 48%) and 160 ($PhthNCH_2$, 100); and then the diadduct **17** (24 mg, 8%) as a colourless oil (Found: 492.1290. $C_{23}H_{23}NO_{10}F$ (M^+–C_2H_5O) requires 492.1274); ν_{max} (CH_2Cl_2) 1 740 (ester C=O) and 1 725 (ketone C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.22–1.36 (12 H, m, 4 x CH_2CH_3), 4.01 (1 H, d, *J* 7 Hz, CHCHCF), 4.21–4.35 (8 H, m, 4 x CH_2CH_3), 4.61 (1 H, dd, *J* 20 and 7 Hz, CHCF), 4.81 and 4.89 (2 H, ABq, *J* 18 Hz, NCH_2CO), and 7.70 and 7.81 (each 2 H, dd, *J* 5.5 and 3 Hz, Ar**H**); δ_C (100 MHz, $CDCl_3$) 13.7, 13.8, and 13.9 (OCH_2CH_3), 48.1 and 51.0 (NCH_2 and CHCHCF), 51.1 (d, *J* 24 Hz, CHCF), 62.6, 62.7. 63.47 and 63.52 (OCH_2), 93.3 (d, *J* 210 Hz, CF), 123.4, 132.1, and 134.0 (aromatics), 164.2 and 164.7 (d, *J* 25 Hz, CFCO), 166.6, 167.20, and 167.23 (CHC=O and NC=O), and 198.3 (ketone); *m/z* (EI) 492 (M^+–C_2H_5O, 82%), 446 (M^+–C_2H_5O–C_2H_5OH, 69), 426 (M^+–C_2H_5O–C_2H_5OH-HF, 33), 311 (65), and 237 (40).

Diethyl allylfluoromalonate **20**

Diethyl fluoromalonate (300 mg, 1.68 mmol) was added dropwise to a suspension of sodium hydride (60% dispersion in oil; 68 mg, 1.70 mmol) in dry DMF (10 ml) stirred under argon at room temperature. After 3 h, freshly distilled allyl bromide (141 µl, 1.63 mmol) was added. After 16 h, water was added and the mixture was extracted with ether. Chromatography, eluting with ether/hexane (1:4), gave the allylfluoromalonate **20** as a colourless oil (255 mg, 70%) (Found: 218.0971. $C_{10}H_{15}O_4F$ requires 218.0988); ν_{max} (thin film) 1 750 (C=O) cm^{-1}; δ_H (400 MHz, CD_2Cl_2) 1.20 (6 H, t, *J* 7 Hz, CH_2CH_3), 2.81 (2 H, ddt, *J* 24, 7, and 1 Hz, CH_2CF), 4.18 (4 H, q, *J* 7 Hz, CH_2CH_3), 5.11 and 5.13 (each 1 H, br d, *J* 10 Hz and *J* 17 Hz resp., $CH=CH_2$), and 5.39 (1 H, ddt, *J* 17, 10, and 7 Hz, $CH=CH_2$); δ_C (100 MHz, CD_2Cl_2) 14.0 (2 x CH_3), 38.8 (d, *J* 21 Hz, CH_2CF), 62.9 (2 x CH_2CH_3), 94.3 (d, *J* 196 Hz, CF), 120.7 ($CH=CH_2$), 129.6 (d, *J* 2 Hz, $CH_2=CH$), and 165.9 (d, *J* 26 Hz, C=O); δ_F (235 MHz, $CDCl_3$) –90.3 (t, *J* 24 Hz); *m/z* (EI) 218 (M^+, 25%), 198 (M^+–HF, 90), 170 (61), and 124 (100).

5-Phthalimidomethyltetrahydrofuran-2-one **30**

Potassium phthalimide (55 mg, 0.30 mmol) was added to a stirred solution of the iodolactone **29** (50 mg, 0.22 mmol) (prepared as in ref. 23) in dry DMF (2 ml) under argon at 50 °C. After 16 h, water was added and the solution was extracted with CH_2Cl_2. Chromatography, eluting with ether/hexane (1:1), gave the lactone **30** as fine prisms (30 mg, 56%) m.p. 167–169 °C (from CH_2Cl_2/ether) (Found: 245.0680. $C_{13}H_{11}NO_4$ (M^+–CO) requires 245.0672); ν_{max} (CH_2Cl_2) 1 780 (lactone C=O) and 1 730 (phthalimide C=O); δ_H

(400 MHz, $CDCl_3$) 2.04 and 2.36 (2 x 1 H, 2 x m, CH_2CH_2CO), 2.57 (2 H, m, CH_2CH_2CO), 3.82 (1 H, dd, *J* 14 and 5 Hz, CH_AH_BN), 4.00 (1 H, dd, *J* 14 and 8 Hz, CH_AH_BN), 4.85 (1 H, qd, *J* 7 and 5 Hz, NCH_2CH), and 7.73 and 7.86 (each 2 H, dd, *J* 5.5 and 3 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 25.4 and 27.9 (CH_2CH_2), 41.3 (CH_2N), 76.6 (NCH_2CH), 123.5, 131.8, and 134.2 (aromatic), 167.9 (2 x N-C=O), and 176.0 (O-C=O); *m/z* (EI) 245 (M^+, 22%), 217 (M^+–CO, 66), 160 (100), and 104 (20).

Methyl 4-hydroxy-5-phthalimidopentanoate **32**

A solution of the lactone **30** (13 mg, 0.048 mmol) was stirred with KOH (20 mg) in MeOH (3 ml) for 1 h, acidified to pH 2, saturated with NaCl, and extracted with EtOAc. The extracts were dried, evaporated, dissolved in MeOH (2 ml), and treated with excess ethereal diazomethane for 15 min. Chromatography, eluting with a gradient of ether (60–100%) in hexane, gave the hydroxy ester **32** as an oil (13 mg, 98%) (Found: 246.0784. $C_{13}H_{12}NO_4$ (M^+–OCH_3) requires 246.0802); δ_H (250 MHz, $CDCl_3$) 1.78 and 1.85 (each 1 H, m, $CH_2CH_2CO_2$) and 2.51 (2 H, m, $CH_2CH_2CO_2$), 2.69 (1 H, br d, *J* 6 Hz, CHOH), 3.66 (3 H, s, OCH_3), 3.77 and 3.78 (each 1 H, d, *J* 5 Hz and 3 Hz resp., NCH_2), 3.93 (1 H, m, CHOH), and 7.72 and 7.84 (each 2 H, dd, *J* 5.5 and 3 Hz, ArH); *m/z* (EI) 246 (M^+–OCH_3, 66%), 190 (100) and 160 (44).

Methyl 4-oxo-5-phthalimidopentanoate **33**

The alcohol **32** (2.0 mg, 0.007 mmol) was stirred in acetone (1 ml) and with 2.67M CrO_3 in 4M H_2SO_4 (2 drops) for 1 h. Dichloromethane (8 ml) was added, the mixture filtered, and the organic layer washed with sat. aq. $NaHCO_3$ then water. Chromatography, with ether/hexane (3:2) as eluant, gave the ketone **33** as an oil (1.8 mg, 96%) (Found: 244.0621. $C_{13}H_{10}NO_4$ (M^+–OCH_3) requires 244.0633); δ_H (250 MHz, $CDCl_3$) 2.66 and 2.84 (each 2 H, t, *J* 6.6 Hz, CH_2CH_2), 3.68 (3 H, s, OCH_3), 4.54 (2 H, s, NCH_2), and 7.72 and 7.86 (each 2 H, dd, *J* 5.5 and 3 Hz, ArH); *m/z* (EI) 244 (M^+–OCH_3, 27%), 216 (M^+–CO_2CH_3, 55), 160 (PhthNCH$_2$, 68), and 115 (100).

2-Fluoropenten-4-oic acid **28**

Diethyl allylfluoromalonate (43 mg, 0.24 mmol) was heated under reflux with sodium chloride (29 mg, 0.48 mmol) in DMSO (1 ml) and water (9 µl, 0.48 mmol) under argon for 4 h. Water was added and the solution was extracted with ether. The combined extracts were dried and then stirred with a solution of KOH (20 mg) in EtOH (1 ml) at room temperature for 1 h. The mixture was acidified with aq. HCl and extracted with EtOAc. Evaporation of the solvent gave the acid **28** (18 mg, 78%) as an oil, pure by t.l.c. (Found: 98.0374. $C_5H_6O_2$ (M^+–HF) requires 98.0380); δ_H (250 MHz, CD_3COCD_3) 2.55–2.84 (2 H, m, CH_2CHF), 2.90 (1 H, br s, OH), 5.06 (1 H, ddd, *J* ca. 50, 7, and 5 Hz, CHF), 5.11 and 5.20 (each 1

H, dd, *J* 10 and 1.5 Hz and *J* 17 and 1.5 Hz resp., CH_2=CH), and 5.85 (1 H, ddt, *J* 17, 10 and 7 Hz, CH_2=C**H**); *m/z* (EI) 98 (M^+–HF, 73%), 73 (66), and 63 (100).

3-Ethoxycarbonyl-3-fluoro-5-hydroxymethyltetrahydrofuran-2-one **35**

A solution of diethyl allylfluoromalonate (200 mg, 0.92 mmol) in acetone/water (9:1; 7 ml) was stirred with a solution of osmium tetroxide (6 mg) in toluene (0.3 ml) and N-methylmorpholine-N-oxide (600 mg, 5.12 mmol) for 16 h. Ether (10 ml) and sodium metabisulphite (ca. 100 mg) were added and after 10 min, the solution was dried ($MgSO_4$) and evaporated. Chromatography, with ether as eluant, gave the lactone **35** as a mixture of diastereoisomers (110 mg, 58%) (Found: 207.0664. $C_8H_{12}O_5F$ (M^++H) requires 207.0659); ν_{max} (CH_2Cl_2) 3 700- 3 300 (OH), 1 795 (lactone C=O), and 1 765 (ester C=O); δ_H (400 MHz, $CDCl_3$) 1.33 (3 H, t, *J* 6.5 Hz, CH_2CH_3), 2.23 (1 H, br s, OH), 2.55–2.94 (2 H, m, CH_2CF), 3.69 and 3.74 (1 H total, 2 x dd, *J* 13 and 4 Hz, CH_AH_BO), 4.01 (1 H, dd, *J* 13 and 3 Hz, CH_AH_BO), 4.34 (2 H, q, *J* 6.5 Hz, CH_2CH_3), and 4.76 and 4.84 (1 H total, 2 x m, CH_2C**H**) ; δ_C (100 MHz, $CDCl_3$) 13.9 (CH_2CH_3), 34.0 and 34.1 (2 x d, *J* 22 Hz, CH_2CF), 62.3 and 62.4 (CH_2OH), 63.4 and 63.5 (CH_2CH_3), 78.0 and 78.9 (CH-O), 92.1 and 92.6 (2 x d, *J* 207 and 198 Hz resp., CF), 165.48 and 165.54 (2 x d, *J* 27 and 29 Hz, ester), and 168.0 and 168.4 (2 x d, *J* 23 and 25 Hz resp., lactone C=O); δ_F (235 MHz, $CDCl_3$) –85.9 (dd, *J* 31 and 24 Hz) and –86.3 (dd, *J* 23 and 6 Hz) (ratio 38 : 62); *m/z* (EI) 207 (M^++H, 22%), 189 (M^+–OH, 9), 119 (19), and 104 (35).

Also isolated, at lower R_f, was the diol **34** (30 mg, 13%) as an oil (Found: 221.0821. $C_9H_{14}O_5F$ (M^+–CH_2OH) requires 221.0817); δ_H (400 MHz, $CDCl_3$) 1.29 (6 H, t, *J* 7 Hz, CH_2CH_3), 1.58 (2 H, br s, OH), 2.27 (1 H, td, *J* 15 and 3 Hz, CH_AH_BCF), 2.46 (1 H, ddd, *J* 30, 15, and 9 Hz, CH_AH_BCF), 3.50 (1 H, dd, *J* 11 and 6 Hz, CH_AH_BOH), 3.66 (1 H, dd, *J* 11 and 3 Hz, CH_AH_BOH), 4.03 (1 H, tq, *J* 6 and 3 Hz, CHOH), and 4.30 (4 H, q, *J* 7 Hz, CH_2CH_3); δ_F (235 MHz, $CDCl_3$) –90.4 (dd, *J* 30 and 15 Hz); *m/z* (EI) 221 (M^+–CH_2OH, 50%), 201 (M^+–CH_2OH–HF, 19), 178 (36), 175 (58), 147 (56), and 91 (100).

3-Ethoxycarbonyl-3-fluoro-5-(trifluoromethanesulphonyloxymethyl)tetrahydrofuran-2-one **36**

Trifluoromethanesulphonic anhydride (40 µl, 0.25 mmol) in dry CH_2Cl_2 (1 ml) was added dropwise over 5 min to a solution of the alcohol **35** (20 mg, 0.10 mmol) in dry CH_2Cl_2 (1 ml) and dry pyridine (20 µl, 0.25 mmol) under argon at –20°C. After 4 h CH_2Cl_2 was added and the solution was washed with cold 1M HCl and then cold water, dried, and evaporated to give an oil (25 mg, 65%), which was found to be sensitive to moisture and hence used directly; ν_{max} (CH_2Cl_2) 1 800 (lactone C=O) and 1 765 (ester C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.34 and 1.35 (3 H total, 2 x t, *J* 7 Hz, CH_2CH_3), 2.58, 2.76, 2.81, and 3.01 (2 H total, 4 x m, CH_2CF), 4.36 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.59, 4.66, 4.75, and 4.76 (2 H total, 4 x m, CH_2OSO_2) and 4.98 and 5.03 (1 H total, 2 x m, CH-O).

3-Ethoxycarbonyl-3-fluoro-5-phthalimidomethyltetrahydrofuran-2-one **37**

To a stirred solution of the triflate **36** (24 mg, 0.063 mmol) in dry DMF (2 ml) under argon at 0 °C was added potassium phthalimide (24 mg, 0.13 mmol). After 16 h at room temperature, water was added and the mixture was extracted with CH_2Cl_2. Chromatography, eluting with ether/hexane (3:2), gave the phthalimide **37** as an oil (7 mg, 33%) (Found: 335.0796. $C_{16}H_{14}NO_6F$ requires 335.0786); ν_{max} (CH_2Cl_2) 1 795 (lactone C=O), 1 770 (ester C=O), and 1 730 (phthalimido C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.32 and 1.34 (6 H total, 2 x t, *J* 7 Hz, CH_2CH_3), 2.51, 2.73, 2.79, and 3.00 (2 H total, 4 x m, CH_2CF), 3.95 (1 H, dd, *J* 14 and 5 Hz, CH_AH_BN), 4.11 and 4.16 (1 H total, 2 x dd, *J* 14 and 7 Hz, CH_AH_BN), 4.32 and 4.34 (2 H total, 2 x q, *J* 7 Hz, CH_2CH_3), 4.99 and 5.05 (1 H total, 2 x m, CH_2CH), and 7.76 and 7.87 (each 2 H, dd, *J* 5.5 and 3 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 13.9 and 14.0 (CH_2CH_3), 36.4 (d, *J* 22 Hz, CH_2CF), 40.8 and 41.1 (CH_2N), 63.5 (CH_2CH_3), 74.85 and 75.0 (CH-O), 91.5 and 91.7 (2 x d, *J* 207 and 200 Hz resp., CF), 123.7, 133.7, and 134.4 (aromatic), 165.14, 165.16, 167.16, and 167.18 (4 x d, *J ca.* 25 Hz, CO_2), and 167.8 (N–C=O); *m/z* (EI) 335 (M^+, 24%), 315 (M^+–HF, 48), 269 (46), 173 (73), and 160 (100).

Methyl 2-fluoro-4-hydroxy-2-methoxycarbonyl-5-phthalimidopentanoate **39**

The lactone **37** (6 mg, 0.018 mmol) was hydrolysed with KOH/MeOH and the resulting diacid esterified as described for lactone **30**, to give the diester **39** (6.5 mg, 100%) as a colourless oil. (Found: 336.0913. $C_{16}H_{15}NO_6F$ (M^+-OH) requires 336.0923); δ_H (400 MHz, $CDCl_3$) 2.32–2.56 (2 H, m, CH_2CF), 2.66 (1 H, d, *J* 6 Hz, CHOH), 3.81 and 3.83 (each 3 H, s, OCH_3), 3.88 (2 H, dd, *J* 12 and 8 Hz, NCH_2), 4.25 (1 H, m, CHOH), and 7.74 and 7.84 (each 2 H, dd, *J* 5.5 and 3 Hz, ArH); *m/z* (EI) 336 (M^+–OH, 13%), 321 (M^+–OH–OCH_3, 49), 301 (M^+–OH–OCH_3–HF, 51), 269 (72), and 160 (100).

Methyl 2-fluoro-2-methoxycarbonyl-4-oxo-5-phthalimidopentanoate **41**

The alcohol **39** (3 mg, 8.5 μmol) was stirred in acetone (1 ml) with 2.67M CrO_3 in 4M H_2SO_4 (2 drops) for 30 min. Methanol (10 drops) was added followed, after the brown colour had disappeared, by acetone (10 ml). The mixture was filtered through Celite, dried, and evaporated to give the fluoroketone **41** as an oil (3 mg, 99%); δ_H (400 MHz, $CDCl_3$) 3.49 (2 H, d, *J* 22 Hz, CH_2CF), 3.84 (6 H, s, OCH_3), 4.52 (2 H, s, NCH_2), and 7.74 and 7.86 (each 2 H, dd, *J* 5.5 and 3 Hz, ArH); *m/z* (FD) 351 (100%).

When a similar oxidation of alcohol **39** (4.5 mg, 12 μmol) was worked up by partitioning the reaction mixture between water and CH_2Cl_2, followed by chromatography, the α,β-unsaturated ketone **40** (2 mg, 46%) was isolated in addition to the fluoroketone **41** (2 mg, 42%) (Found: 301.0590. $C_{15}H_{11}NO_6$ (M^+–CH_2O) requires 301.0594); λ_{max} (MeOH) 351,

291, and 218 nm; δ_H (400 MHz, $CDCl_3$) 3.85 and 3.86 (each 3 H, s, OCH_3), 4.68 (2 H, s, NCH_2), 7.26 (1 H, s, CH=C), and 7.75 and 7.87 (each 2 H, dd, *J* 5.5 and 3 Hz, ArH); *m/z* (EI) 301 (M^+–CH_2O, 28%), 269 (45), 207 (57), and 160 (100).

5-Azidomethyl-3-ethoxycarbonyl-3-fluorotetrahydrofuran-2-one **38**

A solution of triflate **36** (68 mg, 0.177 mmol) and dry sodium azide (50 mg, 0.77 mmol) in dry DMF (2 ml) was stirred under argon for 10 min. Dichloromethane was added and the solution washed with water, dried, and evaporated to give a mixture of the two diastereomeric azides **38** as an oil (45 mg, 59% over two steps from the alcohol **35**) (Found: 188.0496. $C_8H_9O_4F$ (M^+-HN_3) requires 188.0507. Also found: 186.0307. $C_6H_5N_3O_3F$ (M^+-C_2H_5O) requires 186.0299); ν_{max} (CH_2Cl_2) 2 090 (N_3), 1 800 (lactone C=O), and 1 760 (ester C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.31 and 1.32 (3 H total, 2 x t, *J* 7 Hz, CH_2CH_3), 2.47–2.90 (2 H, m, CH_2CF), 3.52, 3.55, 3.70, and 3.71 (2 H total, 4 x dd, *J* 14 and 5 Hz, CH_2N_3), 4.33 and 4.35 (2 H total, 2 x q, *J* 7 Hz, CH_2CH_3), and 4.80 and 4.86 (1 H total, 2 x m, CH-O); δ_C (100 MHz, $CDCl_3$) 13.85 and 13.9 (CH_2CH_3), 35.4 and 35.5 (d, *J* 21 Hz, CH_2CF), 52.6 and 52.7 (CH_2N_3), 63.5 and 63.5 (OCH_2CH_3), 75.5 and 75.7 (CH-O), 91.5 and 92.0 (2 x d, *j* 206 Hz and 199 Hz resp., CF), and 165.1, 165.2, 167.2, and 167.4 (4 x d, *J* 28 Hz, C=O); δ_F (235 MHz, $CDCl_3$) –86.0 (dd, *J* 29 and 24 Hz) and –86.2 (dd, *J* 23 and 7 Hz) (ratio, 44 : 56); *m/z* (EI) 188 (M^+-HN_3, 20%), 186 (M^+–C_2H_5O, 17), 175 (46), 155 (85), 147 (70), and 91 (100).

5-Azidomethyl-3-fluorotetrahydrofuran-2-one **42**

The lactone **38** (40 mg, 0.17 mmol) and sodium chloride (22 mg, 0.37 mmol) were heated under reflux in DMSO (1 ml) and water (10 µl, 0.56 mmol) for 2.5 h. On cooling, water was added and the solution extracted with CH_2Cl_2. The combined organic extracts were washed with water (3 x 10 ml), dried, and evaporated to give the diastereoisomeric lactones **42** (20 mg, 73%) which showed two distinct spots on t.l.c. but were not separated (Found: 159.0448. $C_5H_6N_3O_2F$ requires 159.0452); ν_{max} (CH_2Cl_2) 2 100 (N_3) and 1 795 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.33, 2.40, 2.50 and 2.73 (2 H total, 4 x m, CH_2CF), 3.49, 3.52, 3.65, and 3.75 (2 H total, 2 dd, *J* 13 and 4 Hz, CH_2N_3), 4.56 and 4.82 (2 H total, 2 x m, CH-O), and 5.25 and 5.32 (1 H total, 2 x dt, *J* 42 and 8 Hz, CHF); δ_C (100 MHz, $CDCl_3$) 31.6 and 31.9 (2 x d, *J* 21 Hz, CH_2CHF), 53.3 and 53.8 (CH_2N_3), 74.4 and 75.5 (CH-O), 85.2 and 85.4 (2 x d, *J* 187 Hz and 194 Hz resp., CHF), 170.34 and 170.35 (2 x d, *J* 21 Hz, C=O); δ_F (235 MHz, $CDCl_3$); –114.2 (ddd, *J* 52, 24, and 20 Hz) and –117.5 (ddd, *J* 51, 23, and 7 Hz) (ratio 38 : 62); *m/z* (EI) 159 (M^+, 55%), 103 (M^+–CH_2N_3, 100), and 75 (23).

Methyl 5-azido-2-fluoro-4-hydroxypentanoate **43**

The lactone **42** (16 mg, 0.10 mmol) and KOH (10 mg) were stirred in MeOH (1 ml) at 0 °C for 2.5 h. The solution was then evaporated, acidified with dil. HCl, and extracted with EtOAc. The combined extracts were dried, evaporated, and stirred in MeOH (3 ml) with excess ethereal diazomethane for 10 min. Evaporation gave the hydroxy ester **43** as an oil (16 mg, 83%), homogeneous by t.l.c. (Found: 159.0443. $C_5H_6N_3O_2F$ (M^+–CH_3OH) requires 159.0443); ν_{max} (CH_2Cl_2) 3 700–3 200 (OH), 2 095 (N_3), and 1 730 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.89–2.16 (2 H, m, CH_2CF), 2.46 (1 H, br s, **OH**), 3.28–3.46 (2 H, m, CH_2N_3), 3.79 (3 H, s, OCH_3), 4.02 and 4.08 (1 H total, 2 x m, **CHOH**), and 5.11 and 5.20 (1 H total, dt, *J* 48 and 5 Hz, and ddd, *J* 49, 10, and 3 Hz, resp., **CHF**); δ_C (100 MHz, $CDCl_3$) 36.3 and 36.7 (2 x d, *J* 21 Hz, CH_2CF), 52.5 (OCH_3), 56.6 and 56.9 (CH_2N_3), 66.3 and 66.5 (**CHOH**), 86.0 and 86.1 (2 x d, *J* 183 Hz, **CHF**), and 170.2 (d, *J* 22 Hz, **C**=O); δ_F (235 MHz, $CDCl_3$) –116.6 (dt, *J* 48 and 24 Hz) and –117.6 (ddd, *J* 48, 34, and 17 Hz) (ratio 36 : 64); *m/z* (EI) 159 (M^+–CH_3OH, 12%), 149 (M^+–N_3, 80), 135 (M^+–CH_2N_3, 62), 115 (90), and 103 (100).

Methyl 5-azido-2-fluoro-4-oxopentanoate **44**

The alcohol **43** (14 mg, 0.073 mmol) was stirred with 2.67M CrO_3 in 4M H_2SO_4 (6 drops) in acetone (1 ml) for 5 h. Methanol (0.5 ml) was then added and after 15 min the solution was filtered through a mixture of Celite and $MgSO_4$ and evaporated to give the ketone **44** as an oil (12 mg, 87%), homogeneous by t.l.c. (Found: 158.0375. $C_5H_5N_3O_2F$ (M^+-CH_3O) requires 158.0384); ν_{max} (CH_2Cl_2) 2 090 (N_3), 1 750 (ester), and 1 730 (ketone) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.08 (2 H, dd, *J* 23 and 6 Hz, CH_2CHF), 3.83 (3 H, s, OCH_3), 4.02 (2 H, s, CH_2N_3), and 5.36 (1 H, dt, *J* 47 and 6 Hz, **CHF**); δ_C (100 MHz, $CDCl_3$) 42.0 (d, *J* 22 Hz, CH_2CHF), 52.9 (CH_3O), 57.9 (CH_2N_3), 84.2 (d, *J* 186 Hz, **CHF**), 169.1 (d, *J* 23 Hz, ester), and 199.4 (ketone); δ_F (235 MHz, $CDCl_3$) –115.6 (dt, *J* 46 and 24 Hz); *m/z* (EI) 158 (M^+–CH_3O, 29%), 133 (M^+–CH_2N_3, 47), 113 (48), and 63 (45).

Methyl 5-amino-2-fluoro-4-oxopentanoate hydrochloride **45**

The azido ketone **44** (8 mg, 0.042 mmol) and 10% Pd/C catalyst (5 mg) was stirred in MeOH (2 ml) and concentrated HCl (1 drop) under an atmosphere of H_2 for 4 h, then filtered through Celite and evaporated to give the amine hydrochloride **45** (8.5 mg, 98%), homogeneous by t.l.c.(n-BuOH/H_2O/CH_3CO_2H, 12:5:3). δ_H (400 MHz, CD_3OD) 3.20–3.30 (2 H, br d, *J ca.* 24 Hz, CH_2CHF), 3.79 (3 H, s, OCH_3), 4.04 (2 H, s, CH_2N), and 5.40 (1 H, br d, *J* 47 Hz, **CHF**); δ_C (100 MHz, CD_3OD) 43.0 (d, *J* 22 Hz, CH_2CHF), ca. 49 (CH_2N, obscured by solvent), 53.3 (OCH_3), 85.4 (d, *J* 184 Hz, **CHF**), 170.7 (d, *J* 23 Hz, ester) and 199.8 (ketone); δ_F (235 MHz, CD_3OD) –115.9 (dt, *J* 47 and 23 Hz).

5-Amino-2-fluorolaevulinic acid hydrochloride 3

The ester **45** (3.3 mg, 0.017 mmol) was stirred with 1.8M hydrochloric acid (1 ml) for 36 h and then evaporated to give 2-fluoroALA hydrochloride as a semi-crystalline solid (2.8 mg, 87%), which gave a single, ninhydrin-positive spot at the same R_f as ALA.HCl on t.l.c. (n-BuOH/H_2O/CH_3CO_2H, 12:5:3); δ_H (400 MHz, D_2O) 3.30 (2 H, br d, *J* 24 Hz, CH_2CHF), 4.13 (2 H, s, CH_2N) and 5.34 (1 H, br d, *J* 46 Hz, CHF); δ_C (100 MHz, D_2O) 41.4 (d, *J* 22 Hz, CH_2CHF), 47.0 (CH_2N), 84.5 (d, *J* 194 Hz, CHF), 173.6 (d, *J* 27 Hz, acid), and 200.4 (ketone); δ_F (235 MHz, D_2O) –110.6 (br m).

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