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THE SYNTHESIS OF γ-FLUOROISOLEUCINE*

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SUMMARY

Condensation of 3-fluoro-2-butanone (2) with alkyl diethylphosphonoacetates (4a-d) gave alkyl 4-fluoro-3-methyl-2-pentenoates (5a-d). Addition of bromine yielded alkyl-2,3-dibromo-4-fluoro-3-methylpentanoates (6a,b) which were dehydrobrominated to alkyl 2-bromo-4-fluoro-3-methyl-2-pentenoates (7a,b). Since these compounds could not be hydrogenated to the desired alkyl 2-bromo-4-fluoro-3-methylpentanoates (8a,b), another route was taken. The esters 5a-d were hydrogenated to alkyl 4-fluoro-3-methylpentanoates (11a-c) which were converted to their carbanions. Treatment with bromine gave esters 8a-c, and iodine gave alkyl 4-fluoro-2-iodo-3-methylpentanoates (12a,b). Esters 8a-c and 12a,b were converted to alkyl 2-azido-4-fluoro-3-methylpentanoates (13a-c) whose hydrogenation gave alkyl 2-amino-4-fluoro-3-methylpentanoates (14a-c). Hydrolysis afforded γ-fluoroisoleucine (1).

INTRODUCTION

In our search for cancerostatically active antimetabolites we directed our attention to fluorinated amino acids some of which were reported to show antineoplastic activity [1-4]. One of us synthesized ω-fluoroalloisoleucine which showed some activity in Yoshida tumor [5]. The compound was highly toxic which can be attributed to its biodegradation to fluoroacetic acid [6]. This time we attempted to prepare an isomeric γ-fluoroisoleucine (1) with fluorine in a non-terminal position so that the degradation to the toxic fluoroacetic acid can be precluded.

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We tried a route which included as the first step a reaction of 2-bromo-3-fluorobutane with diethyl acetamidomalonate, diethyl malonate, and ethyl acetoacetate and which is analogous to the successful synthesis of ω-fluoroisoleucine [5]. But, in this case, none of the three alkylations occurred, evidently because elimination of hydrogen fluoride took place during the reaction. Such a reaction is facilitated by the lability of hydrogen on carbon 3 which is rendered acidic by the presence of bromine in the α-position and fluorine in the β-position. [7,8]

Next, we attempted to link together a fluorine-containing moiety with a moiety comprising a masked amino acid grouping. For this purpose the Wittig reaction or, better still, the Horner-Emmons modification [9] using 3-fluoro-2-butanone (2) [10] as the starting material looked very promising. The other component should be alkyl diethylphosphononitroacetate (3a) or alkyl diethylphosphono-N,N-dibenzylaminoacetate (3b). Unfortunately, none of the reactions leading to the intermediates 3a and 3b worked, and this route, too, had to be abandoned.

While all the reactions of 3-fluoro-2-butanone 2 with substituted alkyl diethylphosphonoacetates 3a,b failed, condensation of 2 with simple alkyl diethylphosphonoacetates [11] (4a-d) gave readily alkyl 4-fluoro-3-methyl-2-pentenoates (5a-d) in very good yields. These compounds were considered a good point of departure for the introduction of the amino group into the molecules.

The most straightforward route seemed a reaction of 5a-d with compounds generating a nitronium cation which would combine with the α-carbon to form an α-nitro-α,β-unsaturated ester. However, acetyl nitrate did not react with the ethyl ester 5b, and nitrated the benzene ring in the benzyl ester 5d. Nitric acid and 5b gave a fluorine-free product.

Another possibility of the synthesis of γ-fluoroisoleucine is ammonolysis of the corresponding α-bromoacid. This route was used successfully with many fluorinated α-bromo acids [3,12,13]. To prepare the α-bromoacid, we treated methyl and ethyl 4-fluoro-3-methyl-2-pentenoate (5a,b) with bromine and obtained methyl and ethyl 2,3-dibromo-4-fluoro-3-methylpentanoate (6a and b), respectively. Elimination of hydrogen bromide by refluxing with sodium acetate in methanol afforded methyl and ethyl 2-bromo-4-fluoro-3-methyl-2-pentenoates (7a and b, respectively). But any attempts to reduce these unsaturated esters to methyl and ethyl 2-bromo-4-fluoro-3-methylpentanoates (8a and b), respectively, failed, and the esters were recovered unchanged after treatment with sodium amalgam as well as

$CH_3CHFCH(CH_3)CH(NH_2)CO_2H$

1

$CH_3CHFCOCH_3$

2

$(EtO)_2P(O)CHXCO_2R$

3a: X = NO_2, R = Et

3b: X = $N(CH_2Ph)_2$, R = tert-Bu

$(EtO)_2P(O)CH_2CO_2R$

4a R = Me

b Et

c tert-Bu

d $PhCH_2$

NaH

II

Br_2

$CH_3CHFC(CH_3)=CHCO_2R$ → $CH_3CHFCBr(CH_3)CHBrCO_2R$

5a R = Me

b Et

c tert-Bu

d $PhCH_2$

e H

6a R = Me

b Et

AcONa

$CH_3CHFC(CH_3)=CClCO_2Et$

10

$CH_3CHFC(CH_3)=CBrCO_2R$

7a R = Me

b Et

e H

H_2/catal.

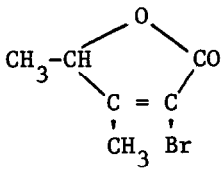
or NaHgx

$CH_3CHFCH(CH_3)CHBrCO_2R$

8a R = Me

b Et

c tert-Bu



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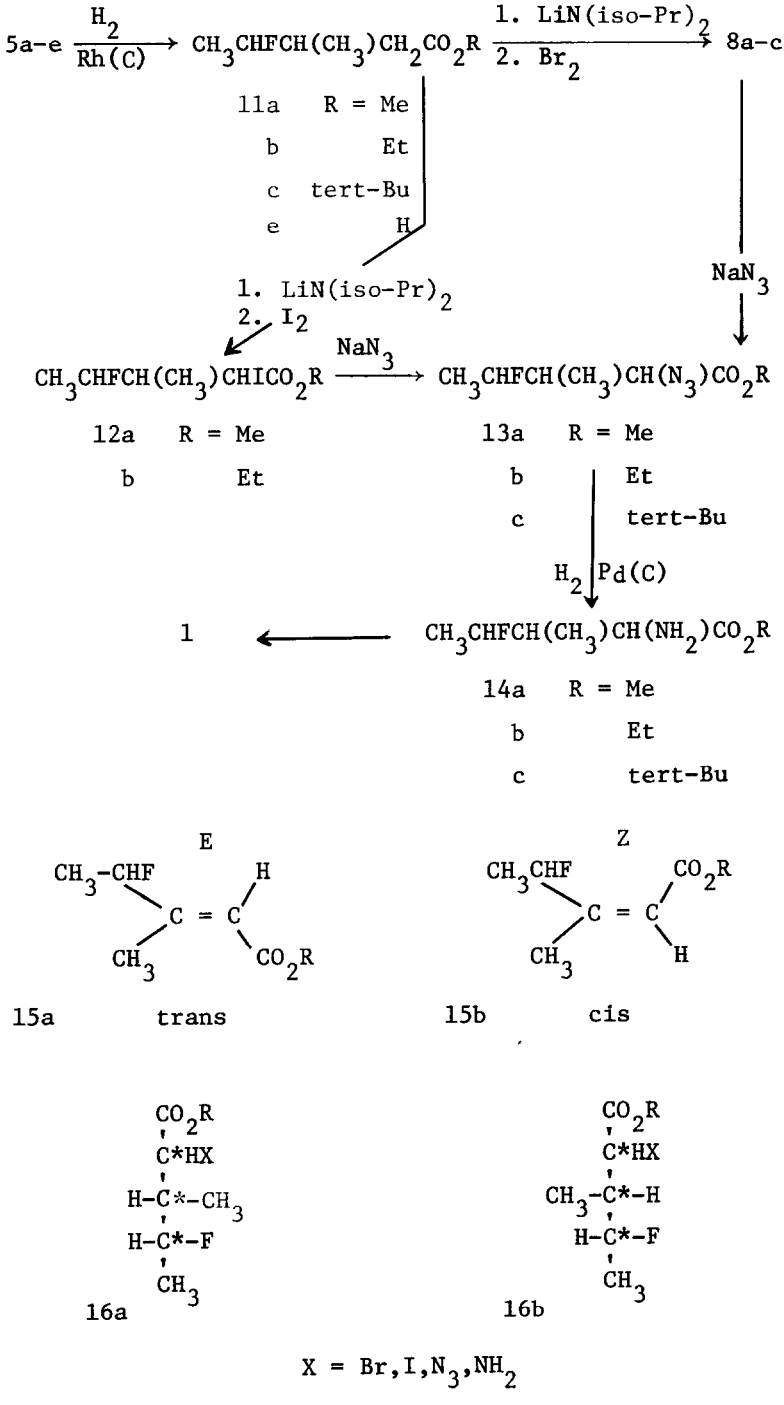
with hydrogen and catalysts under a wide variety of conditions: 10% palladium on activated charcoal, 30% platinum on asbestos, platinum, platinum oxide, and 5% rhodium on alumina or charcoal at 20-80° and 1-75 atm of hydrogen in ether or acetic acid. Hydrogenation of the free acid, 2-bromo-4-fluoro-3-methyl-2-pentenoic acid (7e), obtained by alkaline hydrolysis of the methyl ester 7a, gave γ-lactone of 2-bromo-4-hydroxy-3-methyl-2-pentenoic acid (9), whereas reduction of 7e with sodium amalgam gave an inseparable mixture of 4-fluoro-3-methyl-2-pentenoic acid (5e) and 4-fluoro-3-methylpentanoic acid formed by hydrogenolysis of bromine and subsequent reduction of the double bond. The hydrogenation did not take place even with the sterically less hindered ethyl 2-chloro-4-fluoro-3-methyl-2-pentenoate (10).

When this route failed, an alternative approach was attempted. The unsaturated esters 5a-c were hydrogenated, though not without difficulties, to alkyl 4-fluoro-3-methylpentanoates (11a-c). The benzyl ester 5d gave free acid 11e since hydrogenolysis of the benzyl group took place simultaneously with the saturation of the double bond. The same acid 11e was obtained by hydrogenation of acid 5e which was prepared by alkaline hydrolysis of the methyl ester 5a.

The hydrogenation of the compounds 5a-c had to be carried out under a strict control of the reaction conditions. It did not occur at atmospheric pressure, and at a pressure of 60 atm fluorine was completely hydrogenolyzed. The best conditions were rhodium on alumina or activated charcoal in ether at 4-6 atmospheres at room temperature. When palladium was used and when the temperature during the reaction rose to about 40° one half of the fluoro ester 5a was converted to methyl 3-methylpentanoate.

Preparation of the bromoesters 8 a-c was far from easy. Hell-Volhard-Zelinsky method using the acid 11a and bromine and phosphorus tribromide gave a fluorine-free product. Equally unsuccessful was treatment with N-bromosuccinimide of the chloride of acid 11e [14]. Both these reactions require temperatures around or above 80°, and at this temperature the acid 11e decomposes with a loss of hydrogen fluoride.

Finally, we succeeded in preparing the bromo esters 8a-c by a method described by Rathke et al. [15]. The esters 11a-c were converted to the corresponding carbanions using lithium diisopropylamide in the presence of hexamethylphosphoramide [16], and these were treated with bromine at very low temperatures. In the same way, iodine analogs 12 a and b were prepared by treatment of the carbanions with iodine.


5a-e
H2
Rh(C)
CH3CHFCH(CH3)CH2CO2R
11a R = Me
b Et
c tert-Bu
e H
1. LiN(iso-Pr)2
2. Br2
8a-c
NaN3
1. LiN(iso-Pr)2
2. I2
CH3CHFCH(CH3)CHICO2R
12a R = Me
b Et
NaN3
CH3CHFCH(CH3)CH(N3)CO2R
13a R = Me
b Et
c tert-Bu
H2 Pd(C)
1
CH3CHFCH(CH3)CH(NH2)CO2R
14a R = Me
b Et
c tert-Bu
E
CH3-CHF
H
C = C
CH3
CO2R
15a trans
Z
CH3CHF
CO2R
C = C
CH3
H
15b cis
CO2R
C*HX
H-C*-CH3
H-C*-F
CH3
16a
CO2R
C*HX
CH3-C*-H
H-C*-F
CH3
16b
X = Br,I,N3,NH2

Even though these reactions were carried out at the temperature of Dry Ice, side reactions occurred, especially when larger amounts of the esters were used and the reaction time was long. The best results were obtained when only a few grams of the esters 11a-c were reacted. Even so, the maximum yields we reached were about 15%. In addition, the halogenated esters could hardly be purified. Their separation from the unreacted material was very tedious since heating to temperatures above 100° resulted in a loss of fluorine. Thus, only the ester 8b was prepared pure enough for elemental analysis.

Since the fluorine atom in all the above compounds is very labile we tried to avoid direct ammonolysis using liquid ammonia. Instead, we treated the esters 8a-c with sodium azide in boiling methanol and converted them into the corresponding alkyl 2-azido-4-fluoro-3-methylpentanoates (13a-c).

Catalytic hydrogenation of the azido esters 13a-c gave alkyl 2-amino-4-fluoro-3-methylpentanoates 14a-c. The tert-butyl ester 14c hydrolyzed with trifluoroacetic acid gave trifluoroacetate of γ-fluoroisoleucine 1. The methyl ester 14a evidently still containing some unreacted bromo ester 8a gave, after a 4 week storage at room temperature, hydrobromide of 1 from which 1 was obtained by removal of hydrobromic acid with silver hydroxide.

An attempt has been made to cut the route from 8 to 14 by direct amination of the carbanions derived from 8a and b using hydroxylamine or hydroxylamine-N-sulfonic acid [17]. However, none of the experiments carried out according to the literature gave any amino ester.

Stereochemistry of the Intermediates and Products

Condensations of 3-fluoro-2-butanone 2 with the alkyl diethylphosphonoacetates 4a-d gave mixtures of stereoisomers (15a,b) in which compounds with the bulkier groups in *trans* positions predominated in ratios of 75-80 to 25-20% as determined from the NMR spectra. This is in agreement with the literature [18]. Using repeated fractional distillations we prepared pure E isomer (15a). Hydrogenation of this isomer as well as of the mixture of isomers gave two diastereomers of 8a-c differing in the configuration on carbon 3 in ratios of 46 to 53%. Based on the chemical shifts of hydrogens on carbon 4 it can be concluded that the isomer with the downfield signal (16a) has probably *erythro* configuration on carbon 3 and 4[19].

Bromination or iodination created a third chiral center (on carbon 2) as evidenced by the increase in the number of peaks in gas-liquid chromatography, in ^{19}F NMR and in ^{1}H NMR spectra. The fluorine NMR gave four distinct sets of signals. In proton NMR some signals were uniform whereas some others were very complex.

The presence of so many diastereomers in our intermediates and products made the purification of our compounds very difficult. The boiling points were spread over a wide range, and those of the products partly overlapped with those of the starting materials. This circumstance combined with the thermal instability of most of our compounds caused that we were unable to prepare compounds 13, 14 and 1 in analytically pure form and were using the ir and NMR spectra as the only criteria of identity and purity.

The small amount (0.05 g) of our final product - γ-fluoroisoleucine - consisting of four pairs of enantiomers precluded further purification by crystallization. While our experiments to prepare larger quantity of 1 were underway, Gershon, Shanks, and Clarke [20] published a serendipitous elegant two-step synthesis of 1 which made the continuation of our experiment unnecessary. The NMR spectra of our sample in trifluoroacetic acid compare reasonably well with his spectra in D_2O.

EXPERIMENTAL

Boiling points are uncorrected. Vapor phase chromatography was carried out on a Varian Aerograph model 920 with thermal conductivity detector, helium as a carrier gas, and a 5' x 1/4" stainless steel column packed with 3% SE-30 on 100/120 Varaport 3 using flow rates of 40-60 ml/min at temperatures ranging from 100° to 200°. Elemental analyses were performed on Perkin-Elmer 240 Elemental Analyzer. Infrared spectra were taken on a Beckman IR 20A-X infra-red spectrophotometer using sodium chloride cells for liquid films. Nuclear magnetic resonance spectra were recorded at 100 and 94 MHz for proton and fluorine, respectively, on a JEOL PS-100 high resolution NMR spectrometer using neat liquids or solutions in carbon tetrachloride and hexafluorobenzene as the standard for ^{19}F NMR spectra (upfield shifts being assigned negative values).

Chemicals were of commercial grade and were used without purification. Solvents were dried in a conventional way and, when necessary, distilled before use.

Materials

3-Bromo-2-butanol was prepared from 2,3-epoxybutane [21] or by reduction of 3-bromobutanone with lithium aluminum hydride in ether (56% yield). Bp 62-65° (21 mm). 2-Bromo-3-fluorobutane was prepared from 3-bromo-2-butanol and 2-chloro-1,1,2-trifluorotriethylamine, bp 38-39° (70 mm) (a mixture of erythro- and threo-forms); lit. [22] bp 40-44° (67 mm) (erythro), 48-51° (67 mm) (threo); ^{1}H NMR was in agreement with the literature [22]; ^{19}F NMR: -5.3 and -9.3 (sextets of doublets). 3-Bromo-2-butanone was prepared according to the literature [23] but at a higher temperature (58-85°, yield 75%), bp 67-69° (63 mm). 3-Fluoro-2-butanone 2 was prepared from 3-chloro- or 3-bromo-2-butanone and potassium fluoride [10], bp 74-75°. NMR (neat) δ4.85 (1 H, pair of q, J_{HF} = 50 Hz, J_{HH} = 7 Hz, $\underline{CH}FCH_3$), 2.2 (3H, d, J_{HF} = 5 Hz, $\underline{CH_3}CO$), 1.44 (3H, pair of d, J_{HF} = 25 Hz, J_{HH} = 7 Hz, $\underline{CH_3}CHF$). ^{19}F NMR:-17.5 (sextet of quartets, J_{gem} = 50 Hz, J_{vic} = 25 Hz; $J_{HF}(\underline{CH_3}COCHF)$ = 5 Hz).

Triethyl phosphite, methyl chloroacetate and ethyl chloroacetate were commercial grade reagents. tert-Butyl chloroacetate was prepared from chloroacetyl chloride and tert-butyl alcohol [24], bp 58-59° (18 mm). Lit [24], bp 48-49° (11 mm). Benzyl chloroacetate was prepared from chloroacetyl chloride and benzyl alcohol [25], bp 79-81° (0.1 mm); lit. [25], bp 84-88° (0.4 mm). Alkyl diethylphosphonoacetates (4a-d) were obtained by the Michaelis-Arbuzov reaction from triethyl phosphite and the corresponding chloroacetates [26]. Methyl diethylphosphonoacetate 4a (76-90%), bp 85-87° (0.2 mm); 93-97° (0.15-0.25 mm); lit. [27], bp 127-134° (9 mm). Triethyl phosphonoacetate 4b (94%), bp 146-148° (10 mm); lit. [26] bp 72-80° (0.05 mm). tert-Butyl diethylphosphonoacetate 4c (74%), bp 90-94° (0.3 mm); lit. [28], bp 100-103° (1.5 mm). Benzyl diethylphosphonoacetate 4d (78%), bp 140-144° (0.3 mm); lit. [29], bp 174-179° (1.5 mm).

RESULTS

Alkyl 4-Fluoro-3-methyl-2-pentenoates 5 a-c (nc)

Condensation of 3-fluoro-2-butanone with alkyl diethylphosphonoacetates was carried out analogously to the literature [11] and is exemplified by the synthesis of 5a. To a suspension of 19 g (0.395 mole) of sodium hydride (50% dispersion in paraffin oil) in 600 ml of anhydrous ether 81.5 g (0.39 mol) of methyl diethylphosphonoacetate was added with

stirring and cooling of the flask to 8° with an ice-water bath. Then 35 g (0.39 mol) of 3-fluoro-2-butanone 2 was added dropwise over a period of 20 min while the temperature rose to 24° and a thick oil separated. After stirring the mixture for an additional 45 min 300 ml of water was added, the organic layer was separated, dried with anhydrous magnesium sulfate, and distilled to give 42.3 g (74.5%) of methyl 4-fluoro-3-methyl-2-pentenoate 5a, bp 55.5-67° (10-11 mm) (60% at 55.5-61.5°); ir (neat): 2980, 2940, 1710, 1660, 1430, 1370, 1320, 1280, 1230, 1160, 1070, 1030, 960, 920, 880 (all strong), 800, 730, 590 and 560 (weak) cm^{-1}.

By fractionation using a 20 cm Vigreux column pure E form of 5a (17%) was isolated, bp 69-70° (14 mm). Higher boiling fractions contained small amounts of ethyl 4-fluoro-3-methyl-2-pentenoate formed by trans-esterification during the condensation reaction.

Anal. Calcd. for $C_7H_{11}FO_2$: C, 57.52, H, 7.54. Found: C, 57.42, H, 7.36.

4-Fluoro-3-methyl-2-pentenoic Acid 5e (nc)

A mixture of 1 g (0.0069 mol) of 5a, 4 ml of 2 N potassium hydroxide, 3 ml of water, and 5 ml of methanol was stirred at room temperature for 68 hours. The unreacted ester was removed by ether extraction, the mixture was acidified to Congo Red with concentrated hydrochloric acid, and extracted with two 20 ml portions of ether. Evaporation of the dried ($MgSO_4$) ether extract and distillation of the residue gave 0.5 g (55%) of 5e, bp 49-52° (0.04 mm); ir (neat) 3600-2200 (broad peak, centered at 2950), 1680, 1640, 1410, 1370, 1280, 1240, 1180, 1070, 870 (all strong), 1040, 920, and 690 (weak) cm^{-1}. NMR spectra data of compounds 5a-e are listed in Table 1.

Anal. Calcd. for $C_6H_9FO_2$: C, 54.54, H, 6.86. Found: C, 54.57, H, 7.00.

Alkyl 4-Fluoro-3-methylpentanoates 11a-c (nc)

Catalytic hydrogenation of the compounds 5a-d was carried out at room temperature (18-29°) and 4-5 atm of hydrogen pressure in a stainless steel bomb fitted with magnetic stirring. The catalyst was 5% rhodium on activated charcoal (10% of the amount of the unsaturated compound); 5% of calcium carbonate was added to neutralize hydrogen fluoride which could possibly arise from hydrogenolysis of fluorine. Under these conditions the

Table 1

4-Fluoro-3-methyl-2-pentenoic Acid and Its Esters

Compound	Yield %	Bp.° (mm)	Isomer	^{1}H NMR ∂ (ppm) 1 2 3 3' 4 5 6 7 CH_3-CHF-C(CH_3)=CH-CO-OXY J in Hz						^{19}F NMR
				1 CH_3-	2 -CHF-	3' -(CH_3)	4 =CH-	6 X	7 Y	(HFB)
5a	74	82-84 (28)	E	1.50(3H) pair of d J_{HF}1,2=24 J_{HH}1,2=7	5.05(1H) pair of q J_{HF}gem=48 J_{HH}1,2=7	2.16(3H) s	5.92(1H) s	X=CH_3 3.71(3H) s		-10.4 sextet J_{HF}gem=48 J_{HF}vic=24
		58-62 (12)	Z	1.50(3H) pair of d J_{HF}1,2=24 J_{HH}1,2=7	6.28(1H) pair of q J_{HF}gem=48 J_{HH}1,2=7	2.0(3H) s	5.72(1H) s	X=CH_3 3.71(3H) s		-16.7 sextet of m J_{HF}gem=48 J_{HF}vic=24 $J_{2,3'}$=6
5b	76	72-75 (8)	E	1.96(3H) pair of d J_{HF}1,2=23.5 J_{HH}1,2=7	5.33(1H) pair of q J_{HF}gem=47 J_{HH}1,2=7	2.5(3H) s	6.21(1H) s	X=-CH_2- 4.54(2H) q J_{HH}6,7=7	Y=-CH_3 1.79(3H) t J_{HH}6,7=7	-11.5 sextet J_{HF}gem=47 J_{HF}vic=23.5
			Z	1.96(3H) pair of d J_{HF}1,2=25 J_{HH}1,2=7	6.58(1H) pair of q J_{HF}gem=50 J_{HH}1,2=6	2.4(3H) s	6.0(1H) s	X=-CH_2- 4.54(2H) q J_{HH}6,7=7	Y=-CH_3 1.79(3H) t J_{HH}6,7=7	-18.4 sextet J_{HF}gem=50 J_{HF}vic=25

5c	64.5	40–44 (0.2)	E	1.42(3H) pair of d $J_{HF}1,2=24$ $J_{HH}1,2=7$	4.86(1H) pair of q $J_{HF}gem=48$ $J_{HH}1,2=7$	2.05(3H) s	5.75(1H) s	X=C	Y=$(CH_3)_3$ 1.43(9H) s overlapping 1.42	-9.3 sextet $J_{HF}gem=48$ $J_{HF}vic=24$
			Z	1.42(3H) pair of d $J_{HF}1,2=25$ $J_{HH}1,2=7$	6.13(1H) pair of q $J_{HF}gem=50$ $J_{HF}1,2=7$	1.88(3H) s	5.52(1H) s		Y=$(CH_3)_3$ 1.43(9H) s overlapping 1.42.	-15.8 sextet $J_{HF}gem=50$ $J_{HF}vic=25$
5d	80	104–105 (0.08)	E	1.40(3H) pair of d $J_{HF}1,2=24$ $J_{HH}1,2=6$	4.88(1H) pair of q $J_{HF}gem=48$ $J_{HH}1,2=6$	2.12(3H) s	5.90(1H) s	X=-CH_2- 5.08(2H) s	Y= C_6H_5 7.30(5H) s	-11.2 sextet $J_{HF}gem=48$ $J_{HF}vic=24$
			Z	1.40(3H) pair of d $J_{HF}1,2=24$ $J_{HH}1,2=6$	6.26(1H) pair of q $J_{HF}gem=50$ $J_{HH}1,2=7$	1.92(3H) s	5.7(1H) s	X=-CH_2- 5.08(2H) s	Y=C_6H_5 7.30(5H) s	-17.6 sextet $J_{HF}gem=48$ $J_{HF}vic=24$
5e	55	49–52 (0.04)	E	1.51(3H) pair of d $J_{HF}1,2=24$ $J_{HH}1,2=6.5$	5.04(1H) pair of q $J_{HF}gem=48$ $J_{HH}1,2=6.5$	2.16(3H) s	5.98(1H) s	X=H 12.5 s 12.9		-10.6 sextet $J_{HF}gem=48$ $J_{HF}vic=24$

hydrogenation took place slowly and required 12 to 40 hours depending on the amount of the compound. The yields, bp, and NMR data are listed in Table 2; ir of 11a: 2980, 1730, 1430, 1380, 1280, 1190, 1080, 1050, 1000, and 870 cm^{-1}.

Anal. of 11a. Calcd. for $C_7H_{13}FO_2$: C, 56.74, H, 8.84; Found: C, 56.86, H, 9.11. Anal. of 5c. Calcd. for $C_{10}H_{19}FO_2$ (190.3): C, 63.12, H, 10.07; Found: C, 63.26, H, 10.21.

In one experiment when 15% of 10% palladium on activated charcoal was used and the pressure of hydrogen was 10 atm considerable hydrogenolysis of fluorine took place, and only 27% yield of 11a was obtained beside 42% of methyl 3-methylpentanoate.

4-Fluoro-3-methylpentanoic Acid 11e. (nc)

a) From the benzyl ester 5d

Hydrogenation of 5d over rhodium on activated charcoal gave a 60% yield of a 40/60 mixture of 5e and 3-methylpentanoic acid. Fractionation of the mixture through a 6 cm Vigreux column afforded 11e, bp 40-41° (0.08 mm), a colorless liquid of an unpleasant smell resembling that of isovaleric acid; ir (neat): 3700-2400 (center 2960), 1700, 1450, 1410, 1380, 1290, 1200, 1080, 930, 900, and 870 (all strong); 1050 and 990 (weak) cm^{-1}.

Anal. Calcd. for $C_6H_{11}FO_2$: C, 53.72, H, 8.27; Found: C, 53.72, H, 8.40. NMR data are listed in Table 2.

b) From the unsaturated acid 5e

Hydrogenation of 0.37 g (0.0028 mol) of 5e in 12 ml of ether over 0.05 g of 5% rhodium on activated charcoal in the presence of 0.05 g of calcium carbonate at 5 atm of hydrogen pressure at room temperature over 3 hours gave a quantitative yield of 11e, bp 46.5-48.5° (0.04 mm), identical with that obtained from 5d.

Anal. Found: C, 53.54, H, 8.51.

Methyl 2,3-Dibromo-4-fluoro-3-methylpentanoate 6a (nc)

A solution of 5 g (0.03 mol) (1.6 ml) of bromine in 5 ml of carbon tetrachloride was added dropwise at room temperature to a stirred solution of 4.3 g (0.03 mol) of 5a in 15 ml of carbon tetrachloride over a period of 5 hours. After two days the yellow solution was washed with a solution

Table 2

4-Fluoro-3-methylpentanoic Acid and Its Esters

			^{1}H NMR δ (ppm) 1 CH_3-2 CHF-3 $CH(CH_3)$-3' CH_3-4 CH_2-5 CO-O-6 X-7 Y J in Hz						^{19}F NMR	
Compound	Yield %	Bp.° (mm)	1 CH_3-	2 -CHF-	3' $-CH(CH_3)-$	3 4 $-CH(CH_3)CH_2$	6 X	7 Y	(HFB)	
11a	85	31-34 (0.12)	1.26(3H) pair of d $J_{HF}^{1,2}$=24 $J_{HH}^{1,2}$=6.5	4.50(1H) pair of m J_{HF}^{gem}=48 $J_{HH}^{1,2}$=6.5	0.94(3H) d $J_{3,3'}$=6.5	1.9-2.65(3)	X=CH_3 3.67(3H) s		-12.5 sextet of d J_{HF}^{gem}=48 J_{HF}^{vic}=24 $J_{HF}^{2,3}$=14	-18.8 heptet J_{HF}^{gem}=48 J_{HF}^{vic}=24 $J_{HF}^{2,3}$=0
11b	85	72-76 (20) 31-34 (0.18)	1.1-1.4(6H) m overlapping 7 with $-CH_3$	4.4(1H) pair of m partly overlapping 6 with $-CH_2$-	0.95(3H) d $J_{HH}^{3,3'}$=6	1.8-2.5(3H) m	X=$-CH_2$- 4.07(3.5H) m partly overlapping 2 with -CHF-	Y= CH_3 1.1-1.4(6H) m partly overlapping 1 with CH_3-	-14.4 sextet of d	-21 heptet
11c	95	34-38 (0.25)	1.3 pair of d partly overlapping with $C(CH_3)_3$	4.65(1H) pair of m J_{HF}^{gem}=48	1.0(3H) d $J_{HH}^{3,3'}$=6	1.8-2.6(3H) m	X=C	Y=$(CH_3)_3$ 1.48(9H) s partly overlapping 1 with CH_3-	-13.2 sextet of d	-19.0 heptet J_{HF}^{gem}=48 J_{HF}^{vic}=24
11e	67	threo 46.5-48.5 (0.04)	1.31(3H) pair of d $J_{HF}^{1,2}$=24 $J_{HH}^{1,2}$=6	4.44(1H) pair of quintets $J_{HF}^{1,2}$=48 $J_{HH}^{1,2}$=6	1.0 (3H) d $J_{HH}^{3,3}$=6	1.72-2.8(3H) m	X=H 11.64(1H) s	Y=O	-13.3 sextet of d J_{HF}^{gem}=48 J_{HF}^{vic}=24 $J_{HF}^{2,3}$=14	
		erythro 46.5-48.5 (0.04)	1.29(3H) pair of d $J_{HF}^{1,2}$=24 $J_{HH}^{1,2}$=6.5	4.57(1H) pair of d of q J_{HF}^{gem}=48 $J_{HH}^{1,2}$=6.5 $J_{HH}^{2,3}$=3.5	1.0 (3H) d $J_{HH}^{3,3'}$=6	1.72-2.8(3H) m	X=H 11.64(1H) s			-20.1 heptet J_{HF}^{gem}=48 J_{HF}^{vic}=24

of sodium sulfite, sodium bicarbonate, and with water, dried with magnesium sulfate, and the solvent was stripped off under reduced pressure. Distillation yielded 7.3 g (81%) of 6a, bp 45-48° (0.05 mm).

^{1}H NMR (neat) ∂ 4.76, 4.72, and 4.41 (1H, s, C<u>H</u>Br, partly overlapping the C<u>H</u>F signal), 4.50 (1H, d of multiplets, C<u>H</u>F, partly overlapping the C<u>H</u>Br signal), 3.66 and 3.63 (3H, s, COOC<u>H</u>$_3$), 2.03 and 1.87 (3H, s, CBrC<u>H</u>$_3$) and 1.52, 1.43, and 1.41 (3H, three sets of d of d, $J_{HF\ vic}$ = 23 Hz, J_{HH} = 6 Hz, C<u>H</u>$_3$CHF).

^{19}F NMR: -11.9 (sextet, $J_{HF\ gem}$ = 49 Hz, $J_{HF\ vic}$ = 24.5 Hz), -13.7 (sextet, $J_{HF\ gem}$ = 48 Hz, $J_{HF\ vic}$ = 24 Hz), and -18.2 (sextet, $J_{HF\ gem}$ = 45 Hz, $J_{HF\ vic}$ = 22.5 Hz); ratio of the three peaks = 30:35:35.

Anal. Calcd. for $C_7H_{11}Br_2FO_2$: C, 27.47, H, 3.62. Found: C, 27.92, H, 3.57.

<u>Ethyl 2,3-Dibromo-4-fluoro-3-methylpentanoate 6b</u> (nc)

The ethyl ester 6b was prepared similarly using 13.1 g (0.082 mol) of 5b in 50 ml of carbon tetrachloride and 5 ml (0.094 mol) of bromine added dropwise at 4°. After 4 days at room temperature 25 g (95%) of 6b, bp 60-64° (0.08 mm) was isolated.

^{1}H NMR: ∂ 4.9-3.9 (4H, m, CHF, CHBr, and COOC<u>H</u>$_2$CH$_3$), 2.08 and 1.95 (3H, s, CBrCH$_3$), and 1.75-1.05 (6H, m, CHC<u>H</u>$_3$ and COOCH$_2$C<u>H</u>$_3$).

^{19}F NMR: -7.8 (sextet), -9.6 (sextet and m), and -14.4 (sextet).

<u>Methyl 2-Bromo-4-fluoro-3-methyl-2-pentenoate 7a</u> (nc)

A solution of 7.2 g (0.024 mol) of the dibromide 6a in 20 ml of methanol was stirred and refluxed with 2.1 g (0.026 mol) (9% excess) of anhydrous sodium acetate. After 8 hrs the reaction mixture was evaporated under reduced pressure, the salts were dissolved in 15 ml of water, the organic layer was separated, the aqueous was extracted with two 15 ml portions of dichloromethane, the combined extracts were washed with a solution of sodium bicarbonate, with water, dried with magnesium sulfate, and evaporated under reduced pressure. Distillation yielded 4.3 g (81.5%) of 7a, bp 30-34° (0.035 mm); ir 2990, 2970, <u>1710</u>, 1610, 1430, 1370, <u>1250</u>, 1180, 1020, 890, and 780 cm^{-1}.

^{1}H NMR (CCl_4): ∂ 5.75 and 5.48 (1H, two sets of d of q, $J_{HF\ gem}$ = 50 Hz, J_{HH} = 6.5 Hz, CH$_3$C<u>H</u>F), 3.68 (3H, s, COOCH$_3$), 2.00 (3H, two d, J = 2 Hz,

C($\underline{CH}_3$)), and 1.43 and 1.41 (3H, two sets of d of d, $J_{HF\ vic}$ = 23.5 Hz, J_{HH} = 6.5 Hz, $\underline{CH}_3CHF$).
^{19}F NMR: -10.3 (sextet of q, $J_{HF\ gem}$ = 46 Hz, $J_{HF\ vic}$ = 23 Hz, J_{HH} = 2 Hz, and -17.2 (sextet of q, $J_{HF\ gem}$ = 47 Hz, $J_{HF\ vic}$ = 23.5 Hz, J_{HH} = 2.5 Hz); ratio of the two isomers 62:38.
Anal. Calcd. for $C_7H_{10}BrFO_2$: C, 37.35, H, 4.48. Found: C, 37.39, H, 4.83.

Ethyl 2-Bromo-4-fluoro-3-methyl-2-pentenoate 7b (nc)

The ethyl ester 7b was prepared analogously to 7a by refluxing 14 g (0.044 mol) of 6b, 4 g (0.048 mol) of sodium acetate, and 35 ml of ethanol for 4.5 hours; yield was 8.4 g (80%), bp 39-40° (0.08 mm).
^1H NMR: ∂ 5.88 and 5.62 (1H, two sets of d of q, $J_{HF\ gem}$ = 50 Hz, J_{HH} = 6 Hz, CHF), 4.26 (2H, q, $COOC\underline{H}_2CH_3$), 2.08 and 2.06 (3H, two s, $=CC\underline{H}_3$), 1.44 (3H, d of d, $C\underline{H}_3CHF$, partly overlapping $CH_2C\underline{H}_3$), and 1.35 (3H, t, $COOCH_2C\underline{H}_3$, partly overlapping $C\underline{H}_3CHF$). Ratio of the isomers 60:40.
^{19}F NMR: -10.6 (sextet) and -17.0 (sextet).

2-Bromo-4-fluoro-3-methyl-2-pentenoic Acid (7e) (nc)

Methyl ester 7a (4.2 g, 0.019 mol) was dissolved in 25 ml of methanol, and 19 ml (0.019 mol) of 1 N potassium hydroxide was added portionwise at room temperature to the stirred solution. After 20 hours the mixture had pH 7 and contained a small amount of crystals. It was alkalized to phenolphtalein, the methanol was stripped off under reduced pressure, the residue was extracted with two 40 ml of ether, and the ether extract was evaporated in vacuo to give 0.2 g (4.8%) of the unreacted ester 7a. The aqueous part was acidified with hydrochloric acid to pH 3, extracted with 25 ml of ether and 20 ml of dichloromethane, the combined organic extracts were dried with magnesium sulfate, and evaporated under reduced pressure to yield 2.6 g (66%) of crude acid 7e which could not be purified by distillation because it lactonized to 9.
^1H NMR (neat) ∂ 9.30 (2H, s, $COO\underline{H}_2$), 5-6 (m overlapped by impurities, $C\underline{H}F$), 2.10 and 2.04 (3H, s, $=CCH_3$), and 1.43 (3H, d of d, J_{HF} = 21 Hz, J_{HH} = 6 Hz, $C\underline{H}_3CHF$). ^{19}F NMR: -8.7 (sextet and m), -15 (sextet), and -16.8 (multiplet).

Reduction of 2-Bromo-4-fluoro-3-methyl-2-pentenoic Acid 7e

a) Catalytic hydrogenation of 0.48 g (0.0023 mol) of 7e over 0.2 g of platinum oxide in 10 ml of acetic acid at room temperature and 105 atm of hydrogen did not occur. Distillation of the reaction mixture gave 0.2 g (46%) of lactone 9, bp 50-55° (0.08 mm).
^{1}H NMR (CCl_4) ∂ 4.97 (1H, q, $CH_3\underline{CH}$), 2.09 (3H, s, $=CCH_3$), and 1.47 (3H, d, $C\underline{H}_3CH$).

b) Reduction of the acid 7e (0.7 g, 0.033 mol) with 8 g (0.0035 mol) of 2% sodium amalgam in 5 ml of water containing 1.7 ml of 2 N potassium hydroxide gave, after acidification and ether extraction, 0.3 g of a mixture of the acid 5e resulting from displacement of the vinylic bromine by hydrogen, and of 3-methylpentanoic acid formed by the subsequent reduction.

Ethyl 2-chloro-4-fluoro-3-methyl-2-pentenoate 10 (nc)

Ethyl chlorodiethylphosphonoacetate [30] (17 g, 0.066 mol) was added to 2.77 g (0.066 mol) of sodium hydride (57% dispersion in paraffin oil) in ether with stirring and cooling with ice-water bath. The mixture was stirred at room temperature for an additional 30 minutes, treated with 5.9 g (0.066 mol) of 2, refluxed for 2 hours, and quenched with water. The ether layer was dried with magnesium sulfate, the ether was removed under reduced pressure, and the residue was distilled to give 63% yield of 10, bp 42-45° (0.08 mm).
^{1}H NMR: ∂ 5.88 and 5.60 (1H, two pairs of q, J_{HF} = 50 Hz, J_{HH} = 6 Hz, $C\underline{H}F$), 4.16 (2H, q, $COOC\underline{H}_2CH_3$), 2.07 and 1.90 (3H, two d, $C\underline{H}_3C=$), and 1.52-1.0 (6H, d of d and t, $C\underline{H}_3CHF$ and $COOCH_2C\underline{H}_3$). ^{19}F NMR: -11.5 (sextet) and -18 (sextet). Ratio of the two isomers was 37:63.

Methyl 2-bromo-4-fluoro-3-methylpentanoate 8a (nc)

In a 100 ml three-necked flask fitted with a magnetic stirrer, an argon inlet and outlet, a thermometer, and a septum, 10 ml of 1.7 M solution of butyl lithium (0.017 mol) in hexane was placed under argon, and the flask was cooled with an ice-salt bath to 0°. A solution of 1.7 g (0.017 mol) of diisopropylamine in tetrahydrofuran was added at 0-5°. The reaction mixture was cooled to -78° with a Dry-Ice acetone bath, and 2.5 g

(0.017 mol) of 11a was added with a hypodermic syringe over a period of 10 minutes at -70 to -65°. Hexamethylphosphoramide (2.5 ml) was injected into the reaction mixture to solubilize the lithium salt [16], and the reaction mixture was allowed to warm up to room temperature. It was then added portionwise to a solution of 1.1 ml (3.5 g, 0.022 mol) of bromine (28% excess) in 10 ml of tetrahydrofuran at -70 to -60°. After 20 minutes 20 ml water was added, the solution was acidified with hydrochloric acid, decolorized by shaking with a solution of sodium sulfite, the organic layer was separated, the aqueous layer was extracted three times with 20 ml of ether, the ether extract was dried with magnesium sulfate, and evaporated under reduced pressure. Distillation of the residue gave 1.3 g of the recovered ester 11a (in Dry Ice trap), and 0.6 g of product, distilling at 29-35° at 0.04 mm and composed of 1 part of the recovered ester 11a and 2 parts of 8a. Yield of 8a was 10% (26% based on the reacted ester), ir: 3440(w), 2920, 2850, 1710, 1460, 1370, 1250(w), 1070, 1020, 890(w), and 740(w) cm^{-1}.
^1H NMR: (neat) ∂ 5.2-4.0 (2H, m, CHF and CHBr), 3.73 (3H, s, $COOCH_3$), 2.6-1.8 (1H, m, $C\underline{H}CH_3$), 1.30 (3H, d of d, $C\underline{H}_3CHF$), and 0.91 (3H, d, $C\underline{H}_3CH$). ^{19}F NMR: -9.8 (sextet of d , $J_{HF\ gem}$ = 50 Hz, $J_{HF\ vic}$ = 25 Hz, J_{HH} = 8 Hz), -12.2 (sextet of d, $J_{HF\ gem}$ = 49 Hz, $J_{HF\ vic}$ = 24.5, J = 9 Hz), -23.3 (heptet, $J_{HF\ gem}$ = 49, $J_{HF\ vic}$ = 24.5 Hz), and -30.4 (heptet, $J_{HF\ gem}$ = 51 Hz, $J_{HF\ vic}$ = 25.5 Hz).

Ethyl 2-Bromo-4-fluoro-3-methylpentanoate 8b (nc)

The title compound was prepared analogously in a 16.6% yield, bp 41-45° (0.08 mm).

Anal. Calcd. for $C_7H_{12}BrFO_2$: C, 37.00, H, 5.29. Found: C, 37.48, H, 5.36.
^1H NMR: (neat) ∂ 5.60-4.50 (4H, m, $C\underline{H}Br$, $C\underline{H}F$, and $COOC\underline{H}_2CH_3$), 3.05-2.35 (1H, m, $C\underline{H}CH_3$), 2.05-1.60 (6H, m, $C\underline{H}_3CHF$ and $COOCH_2\underline{CH}_3$), and 1.50 (3H, d, $CH\underline{CH}_3$). ^{19}F NMR: -9.5 (sextet of d, $J_{HF\ gem}$ = 47 Hz, $J_{HF\ vic}$ = 23.5 Hz, J_{HH} = 8 Hz), -11.9 (sextet of d, $J_{HF\ gem}$ = 51 Hz, $J_{HF\ vic}$ = 25.5 Hz, J_{HH} = 8 Hz), -22.7 (heptet, $J_{HF\ gem}$ = 47 Hz, $J_{HF\ vic}$ = 23.5 Hz), and -29.6 (heptet, $J_{HF\ gem}$ = 50 Hz, $J_{HF\ vic}$ = 25).

tert-Butyl 2-Bromo-4-fluoro-3-methylpentanoate 8c (nc)

The ester 8c was prepared analogously in 16.6% yield, bp 58-59° (0.22 mm).

^{1}H NMR: ∂ 5.2-4.1 (2H, m, CHBr and CHF), 2.5-2.2 (1H, m, CHCH$_3$), 1.5 (9H, s, COOC(CH$_3$)$_3$), and 1.40-0.80 (6H, m, CH$_3$CHF and CHCH$_3$). ^{19}F NMR: -9.6 (m), -12.6 (m), -23.2 (heptet, $J_{HF\ gem}$ = 47 Hz, $J_{HF\ vic}$ = 23.5 Hz), and -30.0 (heptet).

Ethyl 4-Fluoro-2-iodo-3-methylpentanoate 12b (nc)

In the apparatus described sub 8a, 16 ml of a 0.62 M solution of lithium diisopropylamide in tetrahydrofuran (prepared from equimolar amounts of butyl lithium in hexane and diisopropylamine at -78°) was treated with 1.6 g (0.01 mol) of 11b at 0° followed by the addition of 2 ml of hexamethylphosphoramide. The mixture was cooled to -78° and injected with a syringe into a solution of 3.0 g (0.012 mol) of iodine in tetrahydrofuran at -78°. After stirring for 5 minutes at -78° the mixture was quenched with water, the organic layer was separated, the aqueous layer was extracted with ether, the combined extracts were washed with water, with a solution of sodium bisulfite, and dried with magnesium sulfate. Distillation afforded 0.42 g (14.5%) of 12b, bp 46-47° (0.05 mm). ^{1}H NMR: ∂ 5.0-4.0 (4H, m, CHF, CHI, and COOCH$_2$CH$_3$; CH$_2$, q centered at 4.15), 2.5-1.7 (1H, m, CHCH$_3$), 1.5-0.8 (9H, m, CH$_3$CHF, CHCH$_3$, and COOCH$_2$CH$_3$). ^{19}F NMR: -6.4 (sextet of d), -8.8 (sextet of d, $J_{HF\ gem}$ = 49 Hz, $J_{HF\ vic}$ = 24.5 Hz, J_{HH} = 10 Hz), -22.2 (heptet, $J_{HF\ gem}$ = 47 Hz, $J_{HF\ vic}$ = 23.5 Hz), and -26.6 (sextet of d).

Methyl 4-Fluoro-2-iodo-3-methylpentanoate 12a (nc)

The title compound was prepared analogously from 1.95 g 11a. The yield was 3.3 g (91%), bp 50-56° (0.85 mm); the compound contained some non-iodinated material from which it could not be separated by distillatior ir 2940, 2860, 1730, 1450, 1430, 1380, 1260, 1200, 1130 (all strong); 1340, 1070, 1000, 920, and 860 (weak) cm^{-1}.
^{1}H NMR (CCl_4): ∂ 5.2-4.0 (2H, m, CHF and CHI), 3.66 and 3.63 (3H, two s, COOCH$_3$), 2.4-1.7 (1H, m, CHCH$_3$), and 1.50-0.80 (6H, m, CH$_3$CHF and CHCH$_3$). ^{19}F NMR: -9.8, -14.5, -26.2, and -29.8 (all m).

Methyl 2-Azido-4-fluoro-3-methylpentanoate 13a (nc)

a) From the bromo ester 8a

A solution of 2.1 g (0.0093 mol) of 8a in 35 ml of methanol was refluxed with 0.75 g (0.012 mol, 23% excess) of sodium azide for 18 hours.

The mixture was evaporated, the solids dissolved in 13 ml of water, the organic layer was separated, the aqueous layer was extracted twice with 10 ml of ether, the combined ether extracts were dried over magnesium sulfate and distilled to give 0.9 g (51%) of 13a.

b) From the iodoester 12a

Refluxing of 3.4 g (0.0125 mol) of 12a with 1 g (0.015 mol) of sodium azide in 40 ml of methanol for 20 hours gave 2.3 g (98%) of 13a, bp 43-49° (0.6 mm). ir: 3450 (w), 2920, 2850, 2100 (N_3), 1730, 1450, 1380, 1250, 1200, 1130, 1070, 1020, and 920 cm^{-1}.
^1H NMR (neat): ∂ 5.0-4.0 (2H, m, CHF and CHN_3), 3.80, 3.78 and 3.70 (3H, three s, $COOCH_3$), 2.6-1.8 (1H, m, $CHCH_3$), and 1.6-0.9 (6H, m, CH_3CHF and $CHCH_3$). ^{19}F NMR: -9.3(m), -12.4(m), -19.2(m), -24.0 (heptet), and -28.4(m).

Ethyl 2-Azido-4-fluoro-3-methylpentanoate 13b (nc)

Refluxing of a solution of 1.6 g (0.007 mol) of 8b with 0.52 g (0.008 mol) of sodium azide in 30 ml of methanol overnight gave 1.22 g (91%) of 13b, bp 40-42° (0.1 mm).
^1H NMR: ∂ 5.1-3.3 (4H, m, CHF, CHN_3, and $COOCH_2CH_3$), 2.5-1.6 (1H, m, $CHCH_3$), and 1.6-0.6 (9H, m, CH_3CHF, $CHCH_3$, and $COOCH_2CH_3$). ^{19}F NMR: -9.3 and -11.6 (multiplets) and -22.4 and -29.3 (heptets).

tert-Butyl 2-Azido-4-fluoro-3-methylpentanoate 13c (nc)

The title compound was prepared analogously in a 95% yield (undistilled product, very strong band at 2100 cm^{-1}).

Methyl 2-Amino-4-fluoro-3-methylpentanoate 14a (nc)

Hydrogenation of 0.5 g (0.0026 mol) of the crude 13a dissolved in 5 ml of methanol over 0.1 g of 10% palladium on charcoal at room temperature and 6 atm of hydrogen overnight gave 0.3 g (70%) of 14a contaminated with a crystalline material. Treatment of the product with water and dichloromethane and evaporation of the extract gave 0.1 g (23%) of 14a; ir: 3320 (broad), 2960, 1740, 1600, 1520, 1450, 1390, 1290, 1250, 1090, 1050, and 890 cm^{-1}.

^{1}H NMR ($CDCl_3$): ∂ 5.6-4.9 (2H, m, C$\underline{H}$F and C$\underline{H}$(NH_2), 3.69 and 3.59 (3H, s, COOC$\underline{H}_3$), 2.08 (1H, m, C$\underline{H}$CH_3), 1.24 (3H, d of d, C$\underline{H}_3$CHF), and 0.88 (3H, d, CHC$\underline{H}_3$). ^{19}F NMR: -8.0, -11.6, -18.2, -20.6 (multiplets).
HBr salt of 14a: ^{1}H NMR (D_2O): ∂ 5.1-4.0 (CHF, overlapped by DOH, 4.7), 4.27 (1H, d, CHNH_2), 3.76 (3H, s, $COOCH_3$), 2.40 (1H, m, C$\underline{H}$CH_3), 1.32 (3H, d of d, J_{HF} = 27 Hz, J_{HH} = 6 Hz, C$\underline{H}_3$CHF), and 0.93 (3H, d, J = 8 Hz, CHC$\underline{H}_3$).

Ethyl 2-Amino-4-fluoro-3-methylpentanoate 14b (nc)

Catalytic hydrogenation of 13b over 10% palladium on activated charcoal in ethanol at room temperature and 4 atm of hydrogen gave 60% of 14b, bp 38-41% (0.1 mm); ir: broad peak at 3400 cm^{-1}, disappearance of the azide peak at 2100 cm^{-1}.
^{1}H NMR (CCl_4): ∂ 4.70 (one of the d of m, CHF-, 1/2 H), 4.40-3.95 (m, CHF and CHBr, partly overlapping $COOC\underline{H}_2CH_3$), 4.12 (2H, q, $COOCH_2CH_3$), 3.8-3.3 (1H, m, C$\underline{H}$NH_2), 2.7-1.9 (m, C$\underline{H}$ CH_3, overlapping N$\underline{H}_2$), 2.35 (2H, s, N$\underline{H}_2$), 1.20-1.0 (6H, m, C$\underline{H}_3$CHF and $COOCH_2C\underline{H}_3$), and 0.88 (3H, d, CHC$\underline{H}_3$). ^{19}F NMR: -10.6 (sextet of d), -14.0 (sextet of d, $J_{HF\ gem}$ = 52.8 Hz, $J_{HF\ vic}$ = 26.4 Hz, J_{HH} = 12 Hz), -20.8 (heptet, $J_{HF\ gem}$ = 50.8 Hz, $J_{HF\ vic}$ = 25.4 Hz), and -25.1 (heptet), $J_{HF\ gem}$ = 50.8 Hz, $J_{HF\ vic}$ = 25.4 Hz).

tert-Butyl 2-Amino-4-fluoro-3-methylpentanoate 14c (nc)

The title compound was prepared by catalytic hydrogenation of 13c at 30 atm of hydrogen at room temperature over 24 hours in a 60% yield, bp 48-50° (0.1 mm).
^{19}F NMR: -11.0(m), -13.5 (sextet of d), -21.5 (heptet, J = 50,25 Hz), and -23.8 (heptet, J = 50,25 Hz).

γ-Fluoroisoleucine 1

Hydrolysis of 0.5 g of 14a in 25 ml of trifluoroacetic acid at room temperature overnight gave trifluoroacetate of 1, soluble in water, giving a positive ninhydrin test, and showing four sets of signals in ^{19}F NMR spectrum.

The crude amino ester 14a (4 g) prepared by hydrogenation of 13a was stored for one month at room temperature. Meanwhile, 0.37 g of crystals - a mixture of the hydrobromides of 14a and 1 - deposited in the flask. The

crystals giving a positive ninhydrin test were spread over a porous plate, washed with ether, dissolved in deuterium oxide, and the NMR spectrum was taken. ^{19}F NMR: -6.8 (multiplet, HFB ext). The solution was evaporated to dryness (0.3 g), the residue was dissolved in water, treated with silver oxide, and the filtrate after the removal of silver bromide was evaporated to dryness under reduced pressure to give 0.05 g of crystalline crude 1, mp 140-150° (decompn.). Lit. [20]: 202-202.5 (decomp.). ^1H NMR (CF_3CO_2H): 7.50 (3H, broad s, NH_3), 5.25-4.30 (2H, m, CHF and $C\underline{H}NH_3$), 4.07 (s, $COOCH_3$, impurity), 2.60 (1H, m, $C\underline{H}CH_3$), 1.52 (3H, d of d, J_{HF} = 27 Hz, J_{HH}=6 Hz, $C\underline{H}_3CHF$), and 1.22 (3H, d, J = 7 Hz, $CHC\underline{H}_3$). ^{19}F NMR: -5.6(m). Lit. [20]: -, 4.4-5.2 + 3.78, 1.9-2.4, 1.36, 1.13.

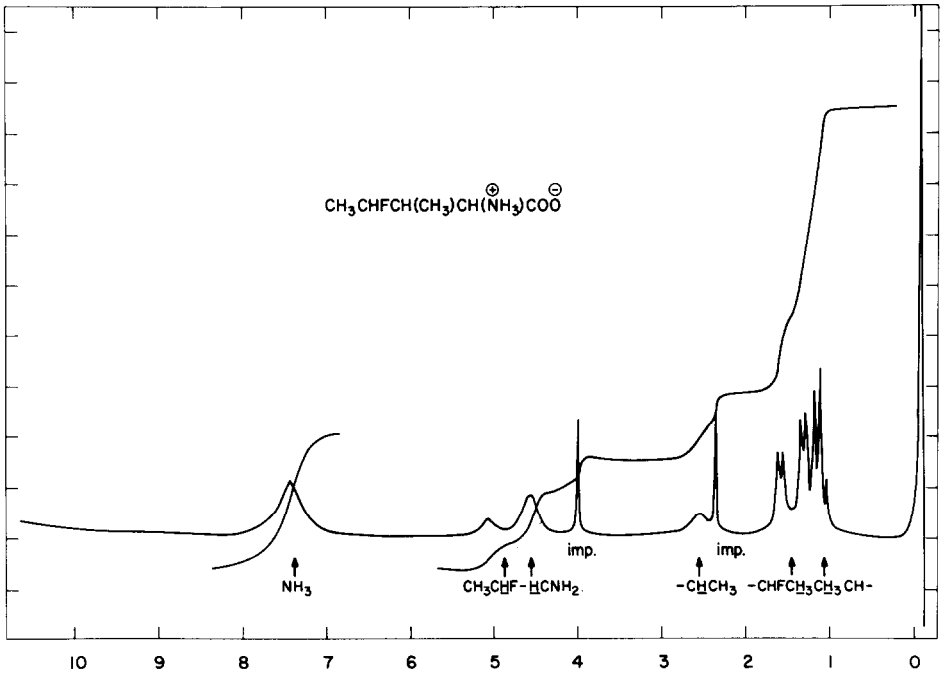


Fig. 1. ^1H NMR spectrum of γ-fluoroisoleucine 1

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