Translated from *Uspekhi Khimii* **60** 1680–1707 (1991) U.D.C. 547.484.2

Aliphatic fluorine-containing amino acids

V P Kukhar', V A Soloshonok
Institute of Bioorganic Chemistry and Petrochemistry
Academy of Sciences of the Ukrainian SSR, Kiev

ABSTRACT. Data on the methods of synthesising fluorine-substituted analogues of the natural aliphatic amino acids are systematised in the review. The increased interest in these amino acids is explained by the wide spectrum of their biological action and also by the possibility of using them to solve theoretical and practical problems in medicine, biochemistry, enzymology, biotechnology and other related scientific areas. Particular attention is paid in the review to preparative methods of synthesis of the fluorine-containing aliphatic amino acids and to the means of obtaining these compounds in an optically pure state.

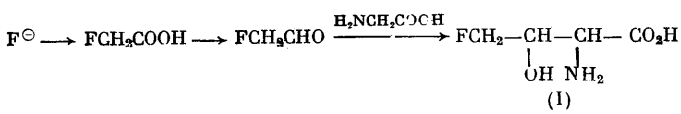
The bibliography contains 120 references.

Contents

I. Introduction 850
II. Preparation of fluorine-containing amino acids by classical methods of amino acid synthesis 851
III. Application of methods of organofluorine chemistry to the synthesis of fluorine-containing amino acids 860
IV. Special methods of obtaining fluorine-containing amino acids 862

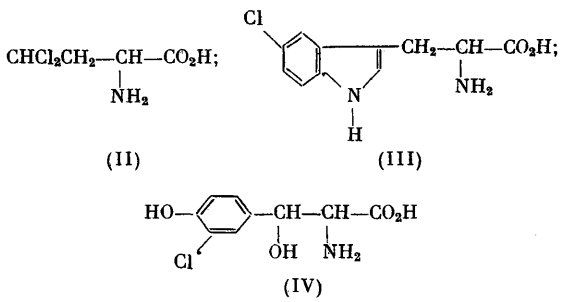
I. Introduction

Until recently fluorine-containing amino acids (FAA) were a unique type of halogen-containing amino acid (AA), having no representatives in nature. Only in 1986 did Japanese investigators[1] describe the first example of FAA biosynthesis, viz. 4-fluorothreonine (I) by the microorganism *Streptomyces cattleya*. It was shown that (I) is a secondary metabolite of monofluoroacetic acid and is formed as follows.



(I)

Chlorine-containing AA, which are the closest analogues of the FAA among halogen-substituted AA, are in contrast fairly widely represented among natural products.[2] The biological activity of chlorine-substituted AA is extremely specific. Many of them are antibiotics or form part of natural peptide or glycopeptide antibiotics. Examples are armentomycin (II), isolated from *Streptomyces armentosus*,[3] 5-chlorotryptophan (III), discovered in the antibiotic longicatenamycin[4] and β-(3-chloro-4-hydroxyphenyl)serine (IV), a structural fragment of the antibiotics actaplanin,[5] vancomycin[6] and aridicin.[7]



(II) (III)

(IV)

All this is a stimulus for broad investigations of other halogen-containing AA.

The most interesting results in the area of halogen-containing AA were obtained when using fluorine atoms for modification, which is explained by the special features of this element compared with the other halogens. Fluorine is the smallest atom after hydrogen and this enables FAA to be incorporated into the metabolism of natural AA (disguise effect).[8,9] On the other hand, the fluorine atom possesses the greatest electronegativity (4.0) of all the elements of the periodic system which is shown in the change of polarisation and an increase in the strength of the C–F bond (451–485 kJ mol^{-1}) compared to the C–H bond (410 kJ mol^{-1}). As a result FAA, incorporated in metabolic processes by organisms by mistake, may in many cases inhibit various metabolic processes partially or completely (blocking effect). The consequences of introducing fluorine atoms into an AA molecule are a change in the acid–base properties of their functional groups and an appreciable increase in the lipophilicity of these compounds, particularly clearly marked when perfluorinated groups are introduced. The manifestation of these factors in the various biochemical processes involving FAA leads to the development of a wide spectrum of biological action. The most important aspects of the biological action of FAA, such as the suicide inhibition of enzymes, the carcinostatic, bactericidal and antiviral activity have been correlated.[10–17]

In addition FAA open the promise of successful application of ^{19}F NMR spectroscopy for the conformational investigation of proteins containing them, of the interaction of AA with receptors, the study of the mechanisms of enzymic reactions,[18,19] and also new routes in biotechnology when selecting microorganisms.[20,21] One rapidly developing use of FAA in medicine is the use of AA labelled with radioactive ^{18}F for the diagnosis of various diseases, the study of pharmacokinetics, the distribution of AA and the products of their metabolism in the tissue and organs of animals and man.[9,22,23]

Intensive study of the biological activity of FAA continually presents synthetic chemists with the problem of developing methods for the synthesis of previously unknown FAA for the testing of biochemical concepts. A second problem is the improvement of methods for obtaining known FAA which may be required in large quantity or in optically pure form.

The methods of synthesis of FAA published up to 1969 have been reviewed.[24,25] The methods of obtaining FAA containing fluorine atoms in the β-position to the amino group have been considered in a recently published review.[26] In addition methods of obtaining FAA have been discussed in studies[10–17] in addition to data on the biological properties of certain FAA. Work discussed in the present review includes the synthesis of fluorine-containing analogues of the natural aliphatic aminocarboxylic acids containing fluorine atoms or fluoroalkyl groups in the carbon skeleton of the AA molecule with the exception of β-fluorine-substituted amino acids.

II. Preparation of fluorine-containing amino acids using classical methods of amino acid synthesis

The possibility of applying classical methods of synthesising AA to obtain aliphatic FAA is determined by the disposition and extent of the effect of the fluorine atoms or fluorine-containing groups on the reaction centres of the molecule and also by the stability of these substituents towards the electrophilic or nucleophilic reagents used. In several cases the influence of fluorine and fluorine-containing groups, which possess a strong electron-accepting effect,[27] proved to be critical for reactions proceeding through the formation of carbocations. However in the majority of cases, when fluorine or the fluorine-containing groups are separated from the reaction centre of the molecule by two or more simple C–C bonds their electronic effects have practically no influence on the course of the reaction. Consequently the classical methods of AA synthesis proved to be suitable for obtaining the majority of fluorine-containing AA.

1. Alkylation of 2-acylaminomalonic acid esters

The classical method of synthesising AA, the alkylation of diethyl 2-acylaminomalonates (AAM) with alkyl halides, has been used for obtaining aliphatic FAA from the first. Alkylation of formamidomalonic ester with 4,4,4-trifluorobutyl iodide or 4,4,4-trifluoro-3-methylbutyl iodide gives the corresponding 6,6,6-trifluoronorleucine (VI) and 6,6,6-trifluoro-5-methylnorleucine (VII).[28]

$$R(CH_2)_2{-}X + R^1{-}CONHCH(COOC_2H_5)_2 \longrightarrow$$
(AAM)

$$\longrightarrow R(CH_2)_2C(COOC_2H_5)_2{-}NH{-}COR^1 \longrightarrow R(CH_2)_2{-}CH(NH_2){-}COOH;$$
(V) (VI)–(XI)

X = Br, I; R^1 = H, CH_3, C_6H_5; R = CF_3CH_2 (VI), $CF_3CH(CH_3)$ (VII), F (VIII), CH_2F (IX), $F(CH_2)_2$ (X), CH_3CHF (XI).

The use of this method for the synthesis of α-amino-ω-fluorocarboxylic acids such as 2-amino-4-fluorobutyric acid (VIII), 5-fluoronorvaline (IX) and 6-fluoronorleucine (X) is complicated. Partial replacement of the fluorine atom by a hydroxyl group occurs with the formation of corresponding α-amino-ω-hydroxycarboxylic acid at the stage of hydrolysing the product of alkylation of the acylmalonic esters (V) with mineral acid.[29,30] Acid hydrolysis of the product (V, R = F) gives a mixture of various quantities of 2-amino-5-fluorobutyric (VIII) and 2-amino-5-hydroxybutyric acids which are separated by crystallisation from aqueous ethanol.[29] It has been shown[30] that on hydrolysis of (V, R = F) a mixture is obtained with a fluorine content from 8 to 39% of the theoretical value for the FAA (VIII).

Replacement of a fluorine atom by an OH group also occurs in the fluoromethylene group and is shown in the preparation of 5-fluoronorleucine (XI).[31,32] 5-Hydroxynorleucine was isolated as well and became the main reaction product on extended heating of compound (V, R = CH_3CHF) with dilute mineral acid.

The synthesis of FAA (IX)–(XI) without contamination by the corresponding hydroxy acids was successfully achieved by hydrolysing the alkylation products (V) with 48% hydrofluoric acid. This approach also enables the preparation of unsaturated aliphatic FAA as was shown in the synthesis of 2-amino-5-fluoro-4,5-dehydroadipic acid (XII).[33]

$$BrCH_2{-}CH{=}CF{-}COOC_2H_5 \xrightarrow[2)\ H_3O]{1)\ AAM} HOOC{-}CF{=}CH{-}CH_2{-}CH(NH_2){-}COOH$$
(XII)

2-Amino-4,4,4-trifluorobutyric acid (XIII), first synthesised[34] in four stages from diazoacetic ester and trifluoroacetic anhydride, may be obtained by the direct alkylation of 2-acetamidomalonic ester with 2,2,2-trifluoroethyl triflate.[35] Attempts to use 2,2,2-trifluoroethyl iodide or 2,2,2-trifluoroethyl tosylate proved to be unsuccessful.

$$CF_3(CH_2)_nOSO_3R \xrightarrow{AAM} CF_3(CH_2)_nC(COOC_2H_5)_2{-}NH{-}COCH_3 \xrightarrow{H_3O^{\oplus}}$$

$$\longrightarrow CF_3(CH_2)_n{-}CH(NH_2){-}COOH$$
(VI), (XIII), (XIV)

n = 1 (XIII), 2 (XIV), 3 (VI); R = CF_3, 4-$CH_3C_6H_4$

5,5,5-Trifluoronorvaline (XIV) is formed similarly from 3,3,3-trifluoropropyl triflate. However, 6,6,6-trifluoronorleucine (VI) is not obtained by the alkylation of 2-acetamidomalonate ester with 4,4,4-trifluorobutyl tosylate. The free (*R*)- and (*S*)-enantiomers of FAA (VI), (XIII), and (XIV) are obtained by enantioselective hydrolysis of their *N*-acetyl derivatives with acylase.

One further method of alkylating acylaminomalonate esters has been used for the synthesis of certain FAA, viz. the Michael addition of activated olefins. 4-Fluoroglutamic acid (XV) is obtained by the condensation of acetamidomalonic ester with the ethyl or methyl esters of 2-fluoroacrylic acid with subsequent acid hydrolysis of the resulting product.[35–38]

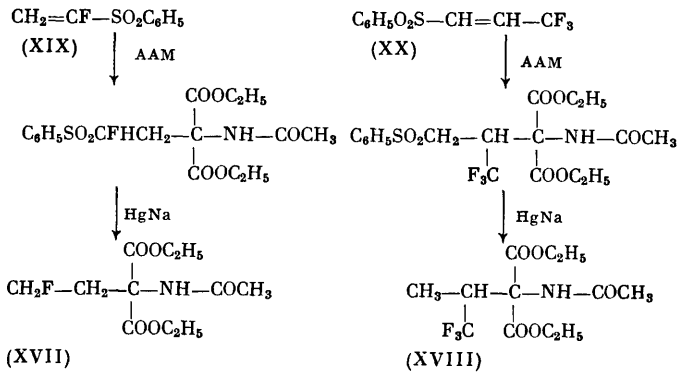
$$CH_2{=}CF{-}COOR \xrightarrow{AAM} C_2H_5OOC{-}CHF{-}CH_2{-}C(COOC_2H_5)_2{-}HN{-}COCH_3 \longrightarrow$$

$$\longrightarrow HOOC{-}CHF{-}CH_2{-}CH(NH_2){-}COOH;\quad HOOC{-}CHF{-}CH_2{-}CH(NH_2){-}CONH_2,$$
(XV) (XVI)

R = CH_3, C_2H_5

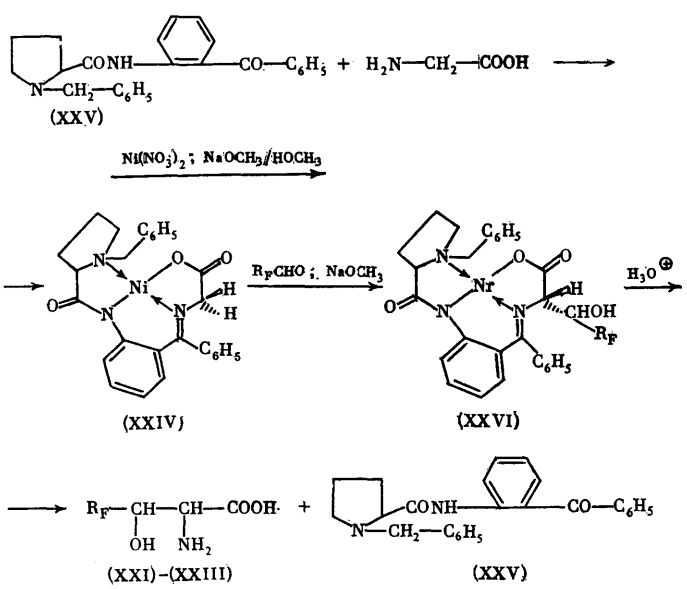
Treatment of the monomethyl ester of 4-fluoroglutamic acid with ammonia gives the corresponding 4-fluoroglutamine (XVI) in low yield.[33]

The ease of removing the benzenesulphonyl group by the action of sodium amalgam on phenyl alkyl sulphones[39] is used in the last stage of synthesising protected 2-amino-4-fluorobutyric acid (XVII)[40] and 4,4,4-trifluorovaline (XVIII).[41] The fluorine-containing vinyl sulphones (XIX) and (XX), readily obtained by the Emmons–Horner reaction from the corresponding benzenesulphonylmethanephosphonates and carbonyl compounds, undergo Michael condensation with 2-acetamidomalonic ester. Subsequent desulphurisation of the resulting products gave FAA derivatives (XVII) and (XVIII) in 40% yield.



2. Alkylation of glycine or its derivatives

A preparative method has been developed recently for the diastereo- and enantioselective synthesis of (*S*)-4,4,4-trifluorothreonine (XXI), (*S*)-*threo*-β-nonafluorobutyl (XXII) and (*S*)-*threo*-β-(ω-hydrododecafluorohexyl)serines (XXIII) using the hydroxyalkylation of the glycine fragment in the chiral Ni(II) complex of its Schiff's base (XXIV) with the appropriate aldehydes.[42]

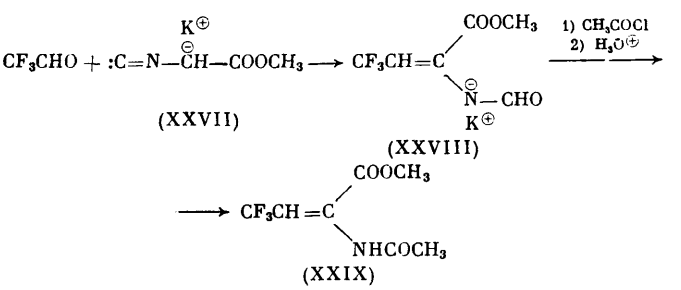


R_F = CF_3(XXI), C_4F_9(XXII), $H(CF_2)_6$(XXIII).

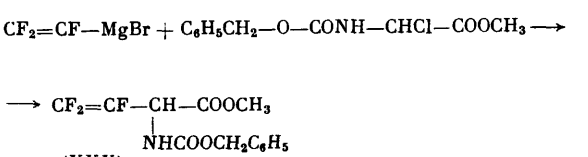
The chiral Ni(II) complex of the glycine Schiff's base is readily assembled from the available (*S*)-2-*N*-(*N*^{1}-benzylprolyl)-*o*-aminobenzophenone (XXV), glycine and nickel nitrate in the presence of sodium methoxide.[43] The hydroxyalkylation of the complex (XXIV) with fluorine-containing aliphatic aldehydes in the presence of sodium methoxide proceeds with high stereoselectivity forming the complex (XXVI) in 70% chemical yield. It was established by X-ray structural analysis that the corresponding FAA (XXI)–(XXIII) with a (2*S*,3*S*)-configuration of the chiral carbon atoms were contained in the complexes (XXVI).

Decomposition of the Ni(II) complexes (XXVI) with 2 N hydrochloric acid gives the free fluorine-containing serines (XXI)–(XXIII) and regenerates the chiral inducing reagent (XXV). It is interesting to record that acetaldehyde gives (*R*)-threonine in the analogous reaction.[44] The total inversion of the stereochemical result of the reaction on using fluorine-containing aldehydes with the complex (XXIV) is apparently linked with the strong influence of the electron-accepting perfluoroalkyl groups on the geminal hydroxyl in the AA fragment formed. In place of the free fluoroaldehydes it is possible to use stable derivatives, such as hydrates or hemiacetals, for the hydroxyalkylation of the glycine-Ni(II) complex. This significantly improves the conduct of the experiment. The diastereoselectivity of the hydroxyalkylation of complex (XXIV) is about 90%. FAA (XXI)–(XXIII) may be obtained with an optical purity of more than 99% after further purification of complexes (XXVI) by chromatography on SiO_2 or by crystallisation.

An interesting example of obtaining fluorine-containing dehydroalanine is shown in the reaction of fluoral with the potassium salt of the isonitrile (XXVII). Acetylation of the intermediate anion (XXVIII) gives a stable imide which is successfully converted regioselectively into the methyl ester of *N*-acetyl-3-trifluoromethyldehydroalanine (XXIX).[45] The electrophilic C=C bond in (XXIX) enables it to be used as a structural unit for obtaining precursors of other FAA.

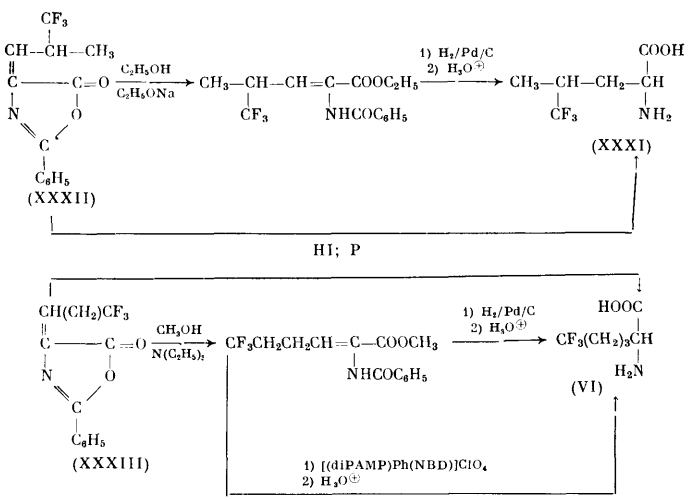


In all the reactions considered above α-anions of glycine or its derivatives and electrophilic fluorine-containing reagents are used. Special mention must also be made of the first example of the use of 'electrophilic glycine' in FAA synthesis. A derivative of α-trifluorovinylglycine (XXX) is obtained in 85% yield by the alkylation of *N*-carbobenzoxy-α-chloroglycine methyl ester with trifluorovinylmagnesium bromide in THF.[46]



3. Azlactone synthesis (the Erlenmeyer reaction)

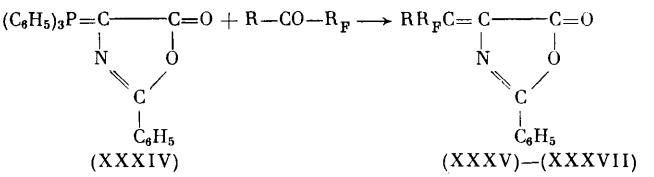
The use of the Erlenmeyer reaction in the synthesis of aliphatic FAA is shown by the preparation of 5,5,5-trifluoroleucine (XXXI) and 6,6,6-trifluoronorleucine (VI).



diPAMP = (1*R*,2*R*)-1,2-bis[(*o*-anisylphenyl)phosphino]ethane, NBD = norborndiene.

A mixture of lead acetate and acetic anhydride in THF is used to form the appropriate azlactones from 2-trifluoromethylpropionic and 4,4,4-trifluorobutyric aldehydes and hippuric acid. This modification enables azlactones (XXXII) and (XXXIII) to be obtained in 100 and 60% yield respectively[47,48] as mixtures of the (*E*)- and (*Z*)-isomers [*E*/*Z* = 13/87 for (XXXII) and *E*/*Z* = 12/88 for (XXXIII)]. The pure (*Z*)-isomers of (XXXII) and (XXXIII) were obtained in 70% yield by crystallisation of the reaction mixture. The pure (*E*)-isomers were isolated by chromatography on SiO_2. The azlactones (XXXII) and (XXXIII) were readily converted by ethanol or methanol in the presence of base into the dehydroaminoacids from which the FAA (XXXI) and (VI) were obtained by reduction with an HI/P mixture. The use of H_2/Pd/C at the reduction stage enabled 5,5,5-trifluoroleucine to be obtained with an 80% excess of the (*S**,*S**)-isomer.[49,50] The optically active methyl ester of *N*-benzoyl-6,6,6-trifluoroleucine was obtained in quantitative yield by the asymmetric hydrogenation of the methyl ester of (*Z*)-*N*-benzoyl-6,6,6-trifluorodehydronorleucine in the presence of a chiral rhodium complex.[48,50] The enantiomeric excess of the corresponding (*S*)-isomer was about 90%.

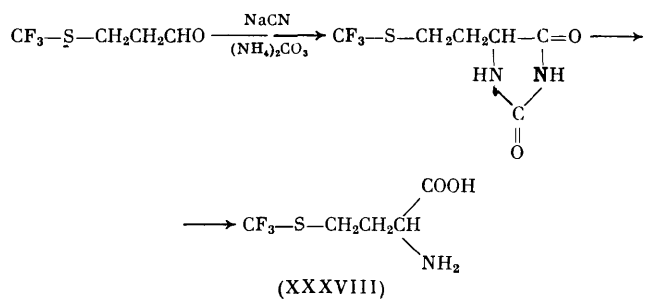
It is possible to use the Wittig reaction between 5-oxo-2-phenyl-4H-oxazolidenetriphenylphosphorane and perfluoroalkyl-containing carbonyl compounds in the synthesis of perfluoroalkyl-containing azlactones.[51] The use of the reagent (XXXIV)[52] enables preparation of the fluorine-containing azlactones (XXXV)–(XXXVII) in far higher yields than using the Erlenmeyer reaction due to the unusual ease of the hydrolytic fission of the azlactone ring in these compounds.[53]



R = R_F = CF_3 (XXXV); R = $COOCH_3$, R_F = CF_3 (XXXVI); R = H, R_F = $CF_2CF_2CF_2CF_2H$ (XXXVII)

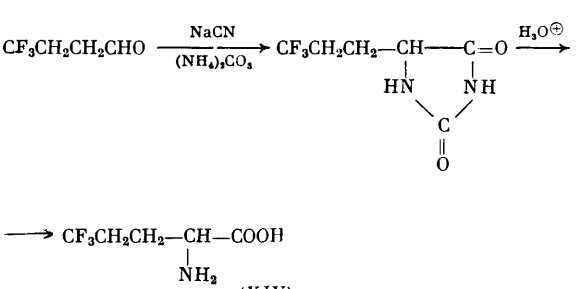
4. Hydantoin synthesis (Bucherer-Bergs reaction)

The synthesis of trifluoromethionine (XXXVIII), a fluorinated analogue of methionine, has been effected with the Bucherer-Bergs reaction.[54] The initial 3-(trifluoromethylthio)propionaldehyde was obtained by addition of trifluoromethyl mercaptan to acrolein.



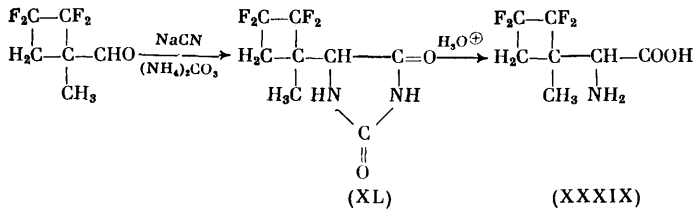
Biological testing showed that trifluoromethionine (XXXVIII) retards the growth of several microorganisms,[55] and is capable of forming *in vivo* the corresponding adenosyl derivative thus inhibiting the demethylation of *S*-adenosylmethionine.[56]

The use of 4,4,4-trifluorobutyraldehyde in the hydantoin synthesis enables preparation of the corresponding 5,5,5-trifluoronorvaline (XIV) in 30% yield.[28]



This approach gives a better result than the Strecker reaction, however in preparative capability it is surpassed by the hydroformylation method, the amidocarbonylation of 3,3,3-trifluoropropene, which is discussed in Section IV.

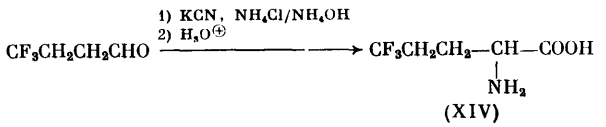
The Bucherer-Bergs reaction has also been used for the synthesis of an unusual AA with a tetrafluorocyclobutyl substituent (XXXIX),[29] in which the hydantoin (XL) is obtained from the corresponding aldehyde in 49% yield. Hydrolysis of hydantoin (XL) with 60% aqueous sulphuric acid gives the FAA (XXXIX).



(XL) (XXXIX)

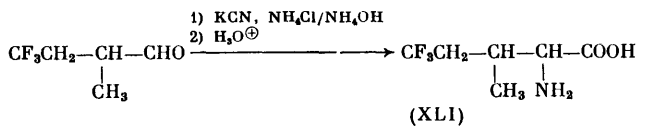
5. Cyanohydrin synthesis (Strecker reaction)

Only β-trifluoromethyl-substituted aldehydes take part in the Strecker reaction. The yield in this case is so low that it does not have the practical value of some of the reactions studied. Thus, 5,5,5-trifluoronorvaline (XIV) is obtained in 4.6% yield by the cyanohydrin method from 4,4,4-trifluorobutyraldehyde.[28]



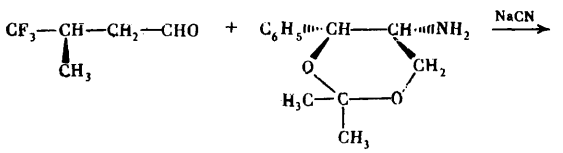
(XIV)

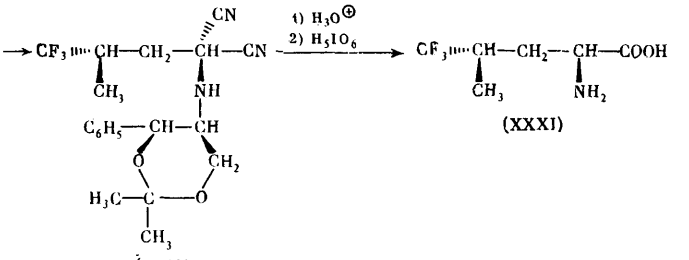
Several methods have been suggested for the preparation of 5,5,5-trifluoroisoleucine (XLI), including the cyanohydrin synthesis based on 2-methyl-4,4,4-trifluorobutyraldehyde.[57] Trifluoroisoleucine (XLI) obtained in this way contains equal quantities of *threo* and *allo* isomers.



(XLI)

The asymmetric synthesis of (2*S*,4*R*)- and (2*S*,4*S*)-5,5,5-trifluoroleucines (XXXI) has been carried out by the Strecker reaction from optically pure 4,4,4-trifluoro-3-methylbutan-1-al and (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxan.[58] The ratio of the (2*S*,4*R*)- and (2*R*,4*R*)-diastereomeric aminonitriles (XLII) was 8:2 (60% enantiomeric excess).

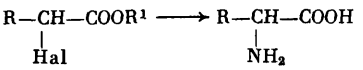




(XXXI) (XLII)

6. Replacement of halogen or hydroxyl group by an amino group.

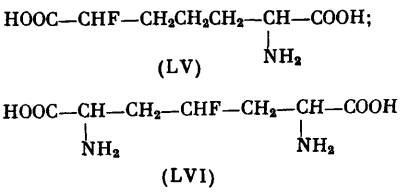
The amination of α-halogen-substituted carboxylic acids is a general method of synthesis for aliphatic FAA. Variants of this approach are manifold. A two stage process is most frequently used. The fluorine-containing α-bromocarboxylic acid or ester is reacted with sodium azide and the azido group is subsequently hydrogenated to an amino group. Another variant is the direct aminolysis of fluorine-substituted α-chloro- or α-iodocarboxylic acids or reaction of them with potassium phthalimide. The choice of experimental conditions is governed by the availability of the fluorine-containing starting material and also by the stability of the functional groups to the action of the reagents used. The following have been obtained by this route: 4-fluoroleucine (XLIII),[59] 4-fluoroisoleucine (XLIV),[60] 5,5,5-trifluoroisoleucine (XLI),[57] β-chlorofluoromethyl- (XLV) and β-chlorodifluoromethylalanine (XLVI),[61] 2-amino-4,4,4-trifluorobutyric acid (XIII),[62] 4,4,4-trifluorovaline (XLVII),[63] 5,5,5,5′,5′,5′-hexafluoroleucine (XLVIII),[64] 2-amino-4-fluorobutyric acid (VIII), 4,4′-difluorovaline (XLIX), 5,5′-difluoroleucine (L), 4-fluorothreonine (I),[65] and several β-perfluoroalkylalanines (LI)–(LIII)[66] and polyfluoronorvalines (LIV) containing in addition bromine or chlorine.[67]



(I), (VIII), (XIII), (XLI), (XLIII)–(LIV

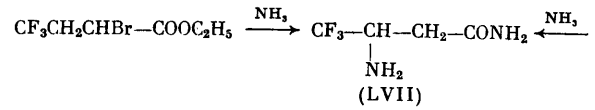
R = $(CH_3)_2CFCH_2$ (XLIII), $CH_3CHFCH(CH_3)$ (XLIV), $CF_3CH_2CH(CH_3)$ (XLI), $CHClFCH_2$ (XLV), $CClF_2CH_2$ (XLVI), CF_3CH_2 (XIII), $CF_3CH(CH_3)$ (XLVII), $(CF_3)_2CHCH_2$ (XLVIII), CH_2FCH_2 (VIII), $(CH_2F)_2CH$ (XLIX), $(CH_2F)_2CHCH_2$ (L), $CH_2FCH(OH)$ (I), $C_2F_5CH_2$ (LI), $C_3F_7CH_2$ (LII), iso-$C_3F_7CH_2$ (LIII), $CF_2XCFXCH_2$, X = Cl, Br, X′ = F, Cl, H (LIV); Hal = Br, Cl, I; R′ = H, C_2H_5.

The fluorine-substituted aminodicarboxylic acids 2-amino-6-fluoropimelic (LV) and 2,6-diamino-4-fluoropimelic (LVI) acids may also be obtained by this method.[68]



(LV) (LVI)

It must be noted that attempts to obtain 2-amino-4,4,4-trifluorobutyric acid (XIII) by the direct aminolysis of ethyl 2-bromo-4,4,4-trifluorobutyrate led to an unexpected product, viz. 3-amino-4,4,4-trifluorobutyramide (LVII),[62] which was obtained by an alternative synthesis from ethyl 4,4,4-trifluorocrotonate (LVIII) and ammonia.[69] The formation of the β-aminoacid (LVII) probably occurs as a result of the dehydrobromination of ethyl 2-bromo-4,4,4-trifluorobutyrate to the ethyl crotonate (LVIII) and subsequent addition of ammonia.[62]

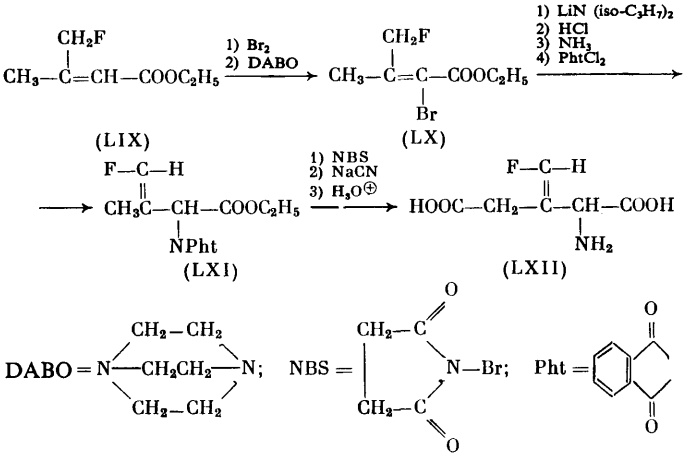


(LVII)

(LVIII)

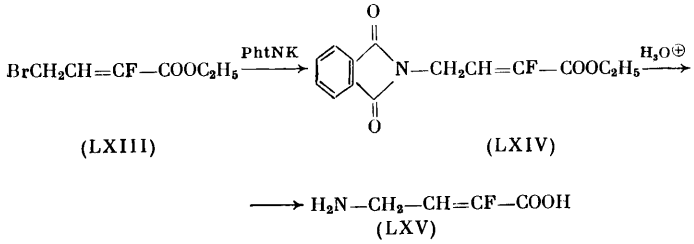
The synthesis of 2-amino-4,4,4-trifluorobutyric acid (XIII) was successfully effected by replacing the bromine atom in ethyl 2-bromo-4,4,4-trifluorobutyrate by an azide group with subsequent reduction over a palladium catalyst.[62]

Replacement of a bromine atom by an amino group has also been used as one of the stages of forming an amino acid molecule in the multistage synthesis of (*E*)-3-fluoromethyleneglutamic acid (LXII).[70]



(LIX) (LX) (LXI) (LXII)

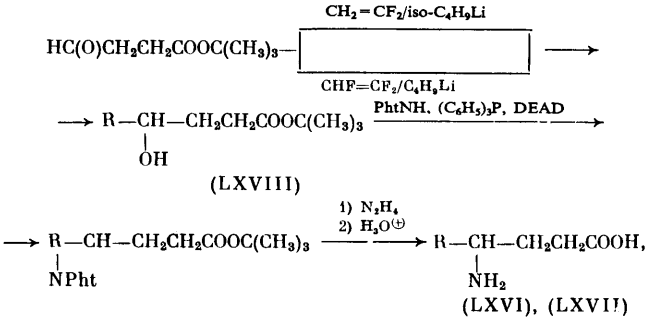
Fluorine-containing aliphatic α-amino acids are generally obtained by replacing a halogen atom by an amino group. Obviously this method is also acceptable for the synthesis of other types of FAA as is shown for the example of obtaining 4-amino-2-fluorocrotonic acid (LXIV) from ethyl 4-bromo-2-fluorocrotonate and potassium phthalimide with subsequent acidic hydrolysis of the product (LXIV).[33]



(LXIII) (LXIV)

(LXV)

Replacement of an OH group by an amino group by the Mitsunobu reaction was used successfully in the synthesis of the γ-difluorovinyl- and γ-trifluorovinyl-substituted γ-aminobutyric acids (LXVI) and (LXVII).[71] The initial hydroxy derivatives (LXVIII) were obtained by the condensation of t-butyl 4-ketobutyrate with difluoro- and trifluoroethylene by the action of iso-butyl- and butyllithium respectively.



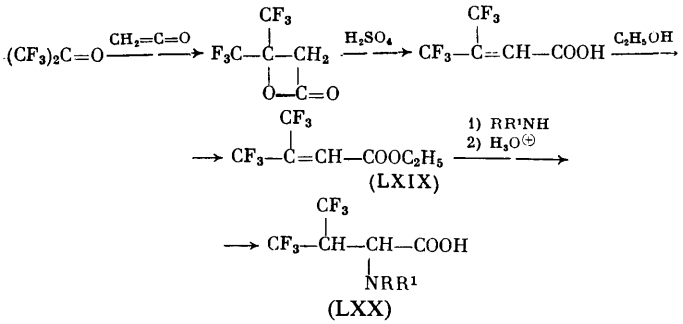
(LXVIII)

(LXVI), (LXVII)

DEAD = $H_5C_2OOC-N=N-COOC_2H_5$; R = $CF_2=CF$ (LXVII), $CF_2=CH$ (LXVI)

7. Addition of ammonia or its derivatives to the double bond of acrylate systems

The addition of ammonia or one of its derivatives to a fluorine-containing acrylic acid, as the final stage in the construction of a FAA molecule, is used mainly to obtain derivatives of hexafluorovaline and α-trifluoromethyl-β-alanine due to the fairly high electrophilicity of the C=C bond in the initial unsaturated acid. Hexafluorovaline (LXX) was synthesised for the first time[72] in preparative yield (80–90%) by the addition of ammonia in ether at −80 °C to ethyl β,β-bis(trifluoromethyl)acrylate (LXIX), which was obtained in three steps from hexafluoroacetone and ketene or by the Wittig reaction.[73]



(LXIX)

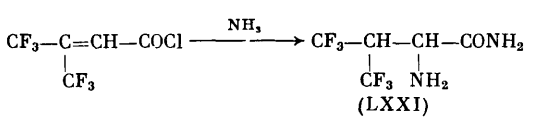
(LXX)

R = R¹ = H (LXX), CH_3, $(CH_2)_4$, $(CH_2)_5$, $CH_2C(CH_3)_2$, $CH_2CHCOOCH_3$; R = H, R¹ = OH; R = H, R¹ = $N(CH_3)_2$; R = H, R¹ = $CH(CH_3)C_6H_5$

Attempts to resolve the hexafluorovaline racemate with enzymes proved unsuccessful.[35,74] This aim was achieved by the crystallisation of the salt of hexafluorovaline (LXX) with *D*-camphor-10-sulphonic acid.[75] Asymmetric synthesis of hexafluorovaline (LXX) in low optical yield may be effected by adding benzylamine to the ester (LXIX) in a solution of methyl *L*-lactate or by the reaction of the optically active *N*-(α-phenylethyl)amide of β,β-bis(trifluoromethyl)-acrylic acid with α-phenylethylamine.[75] It is

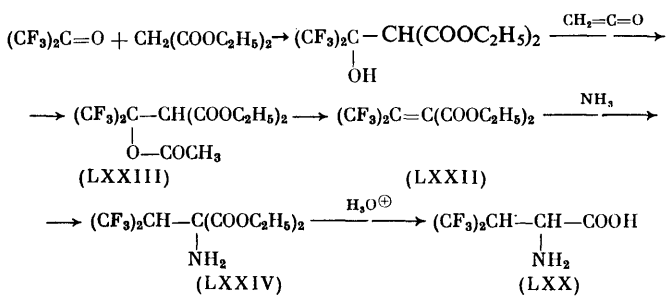
possible to use secondary amines, hydroxylamine and derivatives of hydrazine and aziridine in addition to ammonia in the condensation with the ester (LXIX).[76–79]

Attempts to obtain hexafluorvaline amide (LXXI) by the reaction of ester (LXIX) and ammonia were in vain. Compound (LXXI) was successfully synthesised only by the reaction of ammonia on β,β-bis-(trifluoromethyl)acrylic acid chloride.[72]



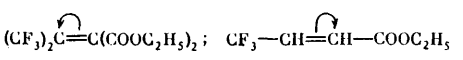
(LXXI)

It is possible to use ethyl α-ethoxycarbonyl-β,β-bis(trifluoromethyl)acrylate (LXXII) instead of ethyl β,β-bis(trifluoromethyl)-acrylate (LXIX) in the synthesis of hexafluorovaline (LXX). The ester (LXXII) is obtained by the low temperature pyrolysis of the *O*-acetyl derivative of the adduct of hexafluoroacetone with ethyl malonate (LXXIII).[80] The addition of ammonia to the diester (LXXII) occurs regioselectively at the α-carbon atom giving the aminodiester (LXXIV), hydrolysis of which gives hexafluorovaline.



(LXXIII) (LXXII) (LXXIV) (LXX)

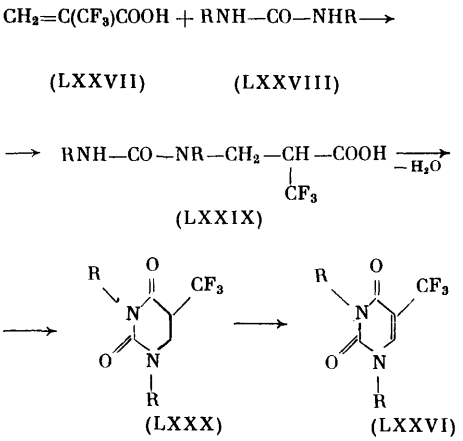
It is interesting to note that in the diester (LXXII) the influence of the two trifluoromethyl groups on the polarisation of the C=C bond proved to be stronger than the action of the two ethoxycarbonyl groups while in ethyl β-trifluoromethylacrylate (LVIII) the reverse polarisation of the C=C bond occurred.[80]



(LXXII) (LVIII)

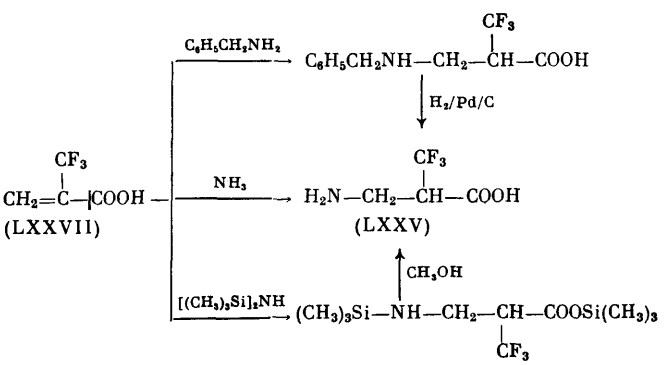
The presence of two trifluoromethyl groups in hexafluorovaline (LXX) is displayed in its physical properties as well as in its biological action. For example hexafluorovaline hydrochloride is insoluble in water.

The development of methods of obtaining α-trifluoromethyl-β-alanine (LXXV) was stimulated by the prospect of synthesising 5-trifluorouracil (LXXVI) from this AA. 5-Trifluorouracil is a fluorinated analogue of thymine and may be used in the synthesis of nucleic acids. The most convenient synthon for obtaining α-trifluoromethyl-β-alanine and its derivatives is seemingly α-trifluoromethylacrylic acid (LXXVII) obtained by the carboxylation of 2-bromo-3,3,3-trifluoropropene. Heating acid (LXXVII) with the ureas (LXXVIII) readily leads to the formation of derivatives of α-trifluoromethyl-β-alanine (LXXIX) which cyclise in the presence of dehydrating agents into the 5-trifluoromethyl-dihydrouracils (LXXX). The conversion of the dihydrouracils (LXXX) into 5-trifluoromethyluracils is effected by bromination and dehydrobromination of the compounds (LXXX).[81,82] Biological testing showed that the derivatives of 5-trifluoromethyluracil possess antiviral activity.



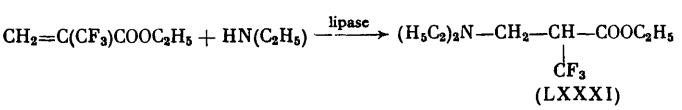
(LXXVII) (LXXVIII) (LXXIX) (LXXX) (LXXVI)

Free α-trifluoromethyl-β-alanine (LXXV) is obtained in high yield by the direct reaction of ammonia with the acid (LXXVII) in methylene chloride at 0–5 °C. Two-stage syntheses through the formation of *N*-benzyl or *N*-trimethylsilyl derivatives have also been studied.[48,50]



(LXXVII) (LXXV)

Asymmetric synthesis of *N,N*-diethyl-α-trifluoromethyl-β-alanine ethyl ester (LXXXI) with a 35% enantiomeric excess has been effected by the condensation of ethyl α-trifluoromethylacrylate with diethylamine in benzene in the presence of lipase modified with lipophilic fluorine-containing compounds.[83]

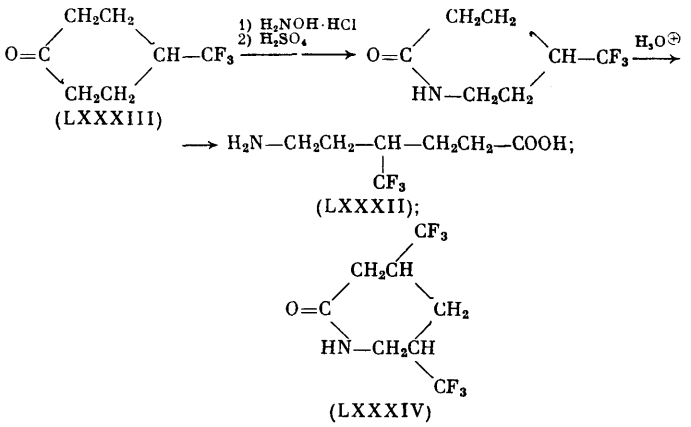


(LXXXI)

8. Beckmann rearrangement

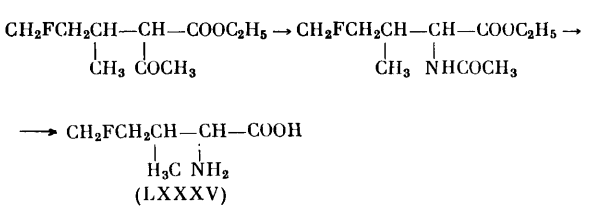
The synthesis of 6-amino-4-trifluoromethylcaproic acid (LXXXII) has been effected from 4-trifluoromethylphenol, which was converted by reduction and oxidation of the resulting alcohol into

4-trifluoromethylcyclohexanone (LXXXIII). The corresponding trifluoromethylcaprolactam was obtained from the ketone (LXXXIII) by the usual scheme of the Beckmann reaction and formed FAA (LXXXII) on acid hydrolysis.[84] The lactam of 6-amino-3,5-bis(trifluoromethyl)caproic acid was obtained from 3,5-bis(trifluoromethyl)phenol in a similar manner.



9. Schmidt rearrangement

The stereoselective synthesis of 5-fluoro-*allo*-isoleucine (LXXXV) has been effected by a Schmidt rearrangement from ethyl 2-acetyl-5-fluoro-3-methylvalerate, which is readily obtained by the alkylation of acetoacetic ester with 3-bromo-1-fluorobutane.[85]

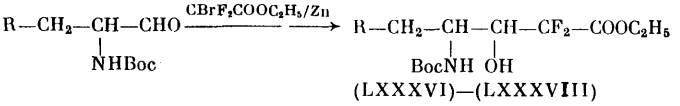


The enantioselective enzymic hydrolysis (using acylase) of the *N*-acetyl derivative of isoleucine (LXXXV) enables the preparation of only the *D*-form of AA (LXXXV) since the *L*-isomer is cyclised under the reaction conditions with replacement of the fluorine atom into *cis*-3-methyl-*L*-proline. It is interesting to note that the preparation of monofluoroisoleucine (LXXXV) by the alkylation of sodium acetamidomalonate with 3-bromo-1-fluorobutane was unsuccessful.[31]

10. Reformatskii reaction

The introduction of ethyl bromodifluoroacetate into the Reformatskii reaction[86] was used in an elegant manner in the synthesis of a 2,2-disubstituted analogue of the unusual AA statin which forms part of the natural pentapeptide pepstatin.[87] Two methods were proposed for the condensation of *N*-t-butyloxycarbonyl-(*S*)-leucinal with bromodifluoroacetic ester in the presence of activated zinc.[88,89] Boiling the reactants in THF gave the *threo*-isomer of (LXXXVI) alone. However partial racemisation (~10%) was observed at the α-carbon atom of the initial leucinal. Conducting the reaction at low temperatures by ultrasound proved to be more preferable and led to the formation of a mixture of the (3*R*,4*S*)- and (3*S*,4*S*)-diastereoisomers of (LXXXVI) (ratio 7 : 3) which was easily separated into the individual isomers. The optically pure diastereoisomers were used in the synthesis of tetrapeptides for study of their ability to inhibit renin, an enzyme playing an important role in the regulation of blood pressure.

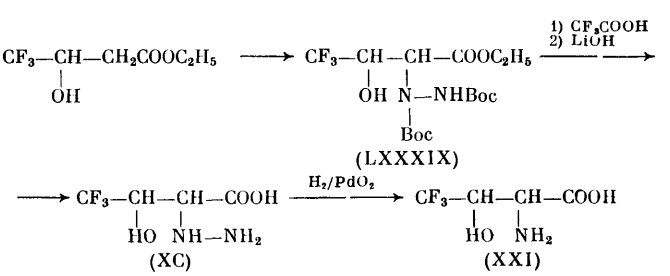
Analogues of difluorostatin containing phenyl (LXXXVII) and cyclohexyl (LXXXVIII) groups in place of the isopropyl group were obtained in a similar manner.[88,89] These compounds were made in order to determine the influence of the lipophilicity of substituents in the *gem* position to the amino group of statin on the biological activity of peptides containing these AA.



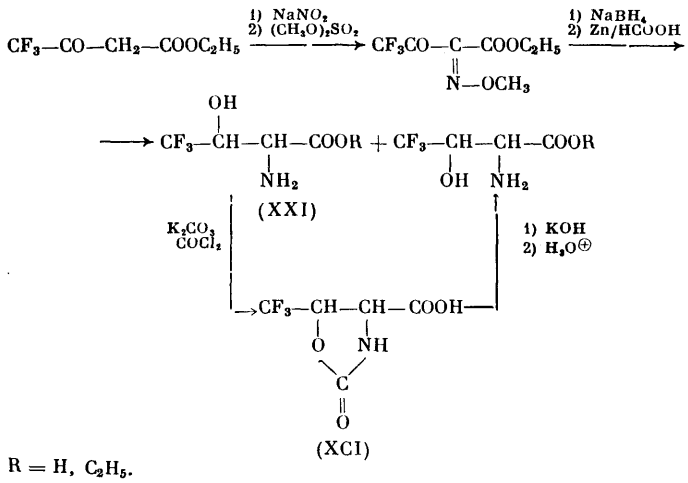
R = iso-C_3H_7 (LXXXVI), C_6H_5 (LXXXVII), cyclo-C_6H_{11} (LXXXVIII); Boc = $COOC(CH_3)_3$

11. Use of other classical methods of AA synthesis to obtain FAA

Several methods have been proposed for the synthesis of trifluorothreonine (XXI) in which 4,4,4-trifluoroacetoacetic ester or products one stage removed from it are used as starting materials. Thus by the sequential action of lithium diisopropylamide and di-t-butyl azodicarboxylate on ethyl 4,4,4-trifluoro-3-hydroxybutyrate a mixture is obtained of diastereoisomers (6 : 1) of protected 4,4,4-trifluoro-2-hydrazino-3-hydroxybutyric acid (LXXXIX), the first representative of the fluorine-containing hydrazinoacids.[90] The free hydrazinoacid (XC), obtained by the hydrolysis of compound (LXXXIX), may be converted readily into trifluorothreonine (XXI) by reduction of the hydrazino group.

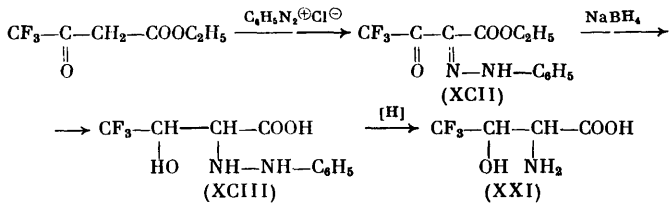


Racemic trifluorothreonine (XXI) has been obtained by the nitrosation of ethyl trifluoroacetoacetate with subsequent methylation of the resulting oxime and reduction of the C=O and C=N bonds.[91] The ratio of *threo* and *allo* isomers in trifluorothreonine (XXI) was 1.5 to 1. Trifluoro-*allo*-threonine may readily be epimerised into the corresponding *threo* isomer through the formation and breakdown of the oxazolidinone (XCI).



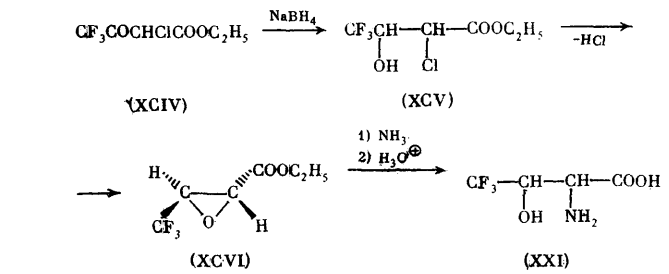
R = H, C_2H_5.

The conversion of the methylene group of 4,4,4-trifluoroacetoacetic ester into an azomethine for subsequent conversion into an amino group may also be carried out by the Japp-Klingeman reaction between 4,4,4-trifluoroacetoacetic ester and phenyldiazonium chloride.

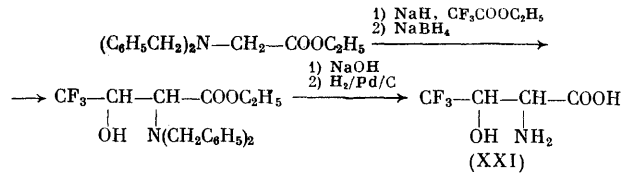


The preparation of 4,4,4-trifluorothreonine (XXI) from phenylhydrazone (XCII) is effected into three stages, viz. reduction of the carbonyl group and azomethine bond, saponification of the ester group and catalytic hydrogenation of the phenylhydrazine (XCIII).[91]

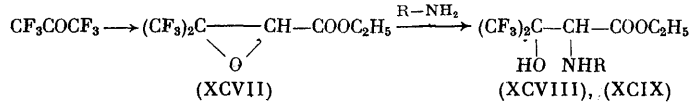
The diastereoselective synthesis of 4,4,4-trifluorothreonine (XXI) is carried out using as precursor ethyl 2-chloro-4,4,4-trifluoroacetoacetate (XCIV), which is readily obtained by the chlorination of 4,4,4-trifluoroacetoacetic ester.[91] The reduction of the carbonyl group of the ester (XCIV) leads to the formation of a mixture of diastereoisomers of ethyl 2-chloro-4,4,4-trifluoro-3-hydroxybutyrate (XCV) in a ratio of 7:4. Dehydrochlorination of hydroxyester (XCV) gives a single compound, the α-oxime (XCVI) to which the *trans*-configuration has been assigned.[91] Decomposition of the oxirane ring of the ester (XCVI) occurs mainly at the α-carbon atom leading to the formation of 4,4,4-trifluoro-*allo*-threonine as an ester or amide depending on the reaction conditions.



An alternative approach, comprising the condensation of ethyl *N,N*-dibenzylglycinate with ethyl trifluoroacetate under the action of sodium hydride and subsequent reduction of the carbonyl group and hydrogenolysis of the *N*-benzyl groups, gave a mixture of the diastereoisomers of trifluorothreonine (XXI) with a predominance of the *allo* form.[92]

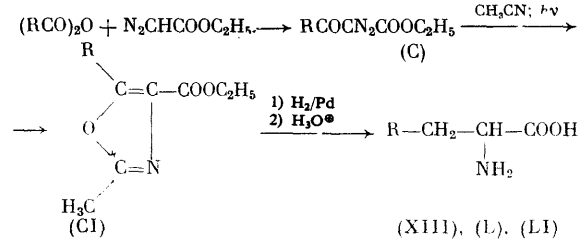


Opening of the oxirane ring with benzylamine or aniline in the bis(trifluoromethyl)glycidic ester (XCVII), obtained from hexafluoroacetone and diazoacetic ester,[93] leads to the formation of the ethyl esters of *N*-benzyl- and *N*-phenyl-4,4,4,4′,4′,4′-hexafluoro-3-hydroxyvaline (XCVIII) and (XCIX) respectively.[94]



R = $C_6H_5CH_2$ (XCVIII), C_6H_5 (XCIX)

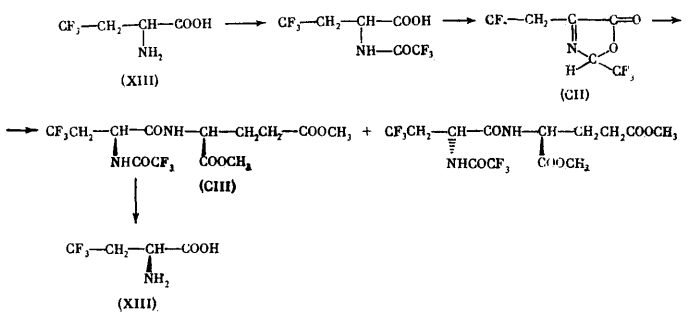
A general method has been developed for the synthesis of β-perfluoroalkylalanines based on the photochemical conversion of the perfluoroacyldiazoacetic esters (C).[34]



R = CF_3 (XIII), C_2F_5 (L), C_3F_7 (LI).

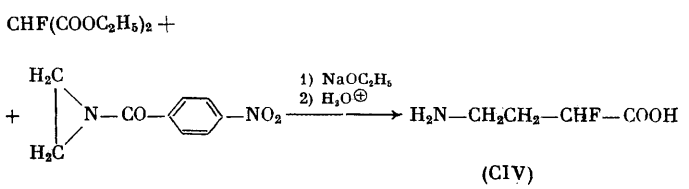
Irradiation of the compounds (C) leads to the formation of the ethyl esters of 2-methyl-5-perfluoroalkyloxazole-4-carboxylic acids (CI) the catalytic hydrogenation of which is accompanied by hydrogenolysis of the C—O bond giving the corresponding esters of *N*-acetyl-AA. Acid hydrolysis of the ethyl esters of *N*-acetyl-3-perfluoroalkylalanines gives 2-amino-4,4,4-trifluorobutyric acid (XIII), 4,4,5,5,5-pentafluoronorvaline (L) and 4,4,5,5,6,6,6-heptafluoronorleucine (LI).

An asymmetric process has been proposed to obtain the *L*-enantiomer of 2-amino-4,4,4-trifluorobutyric acid (XIII) using the racemic FAA (XIII) as starting material. *DL*-2-Amino-4,4,4-trifluorobutyric acid (XIII) was converted into 4-(2,2,2-trifluoroethyl)-2-trifluoromethyl-Δ^3-oxazolin-5-one (CII) by sequential trifluoroacetylation and dehydration by dicyclohexylcarbodiimide.[34]

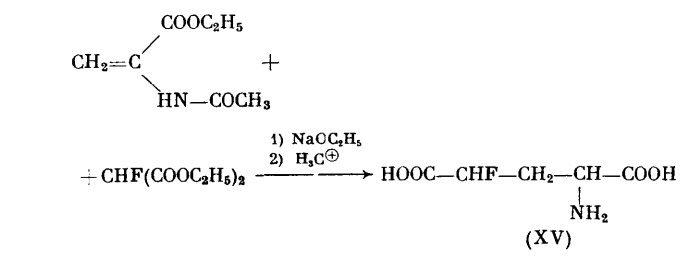


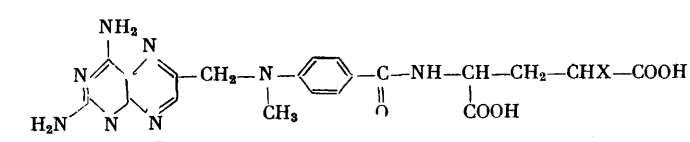
Opening of the oxazolinone ring of (CII) with dimethyl *L*-glutamate gives a mixture of the diastereoisomeric dipeptides (CIII) in a ratio $(L,L):(D,L) = 83:17$. Enantiomerically pure *L*-2-amino-4,4,4-trifluorobutyric acid (XIII) was obtained after numerous crystallisations of the mixture (CIII) with subsequent removal of the *L*-glutamic acid residue.

A convenient method of synthesising γ-amino-α-fluorobutyric acid (CIV) is based on the nucleophilic fission of the *N*-(4-nitrobenzoyl)aziridine anion with monofluoromalonic ester and subsequent saponification of the resulting condensation product.[95]



4-Fluoroglutamic acid (XV), obtained by the addition of fluoromalonic ester to ethyl 2-acetylaminoacrylate, has been used for the synthesis of the fluorinated analogue (CVI, X=F) of the known antitumour compound methotrexate (CVI, X=H) [35,38,96,97] which has been proposed for the treatment of leukaemia.[98]

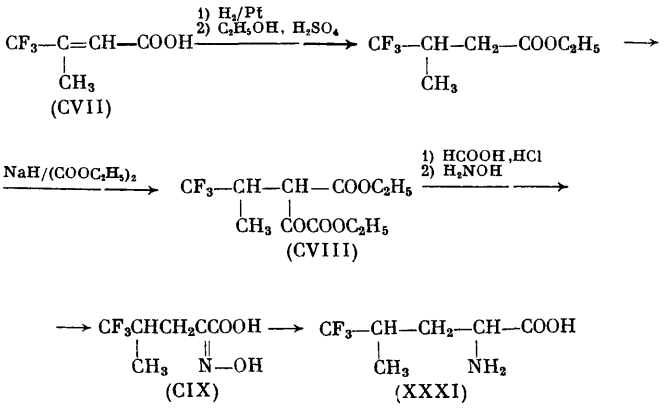




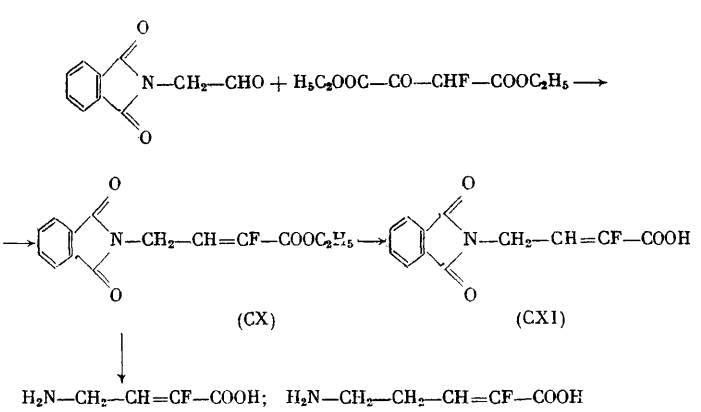
(CVI), X=H, F

It must be noted that this method gives a higher yield of FAA (XV) than the alternative Michael addition of ethyl 2-fluoroacrylate of acetamidomalonate.[35-37]

A multistage method has been proposed for obtaining 5,5,5-trifluoroleucine (XXXI) in which 4,4,4-trifluorocrotonic acid (CVII) is used as starting material.[99] The ketoester (CVIII) is synthesised from it by hydrogenation, esterification and condensation with diethyl oxalate. This is converted into the oxime (CIX) after hydrolysis of the ester groups and decarboxylation. Catalytic hydrogenation of the oxime (CIX) gives the desired AA, 5,5,5-trifluoroleucine (XXXI).



4-Amino-2-fluorocrotonic acid (LXIII) is obtained by boiling phthalimidoacetaldehyde with the sodium derivative of diethyl 2-fluoro-3-ketosuccinate in xylene, as a result of which compound (CX) is formed. Hydrolysis of it with dilute hydrochloric acid gives 2-fluoro-4-phthalimidocrotonic acid (CXI) but the use of concentrated HCl leads to the FAA hydrochloride (LXIII).



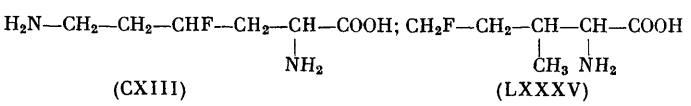
3-Phthalimidopropanal may be converted into 5-amino-2-fluoropent-2-enoic acid hydrochloride (CXII) in a similar manner.[100]

III. Application of methods of organofluorine chemistry to the synthesis of fluorine-containing amino acids

The application of the methods of organofluorine chemistry to the synthesis of aliphatic FAA is linked mainly with the possibility of introducing fluorine atoms and fluorine-containing groups directly into an already prepared AA and has certain advantages in some cases over the classical AA syntheses. For example replacement of hydrogen atoms by fluorine or fluoroalkyl groups in the side chain of an AA may be effected without affecting the chiral α-carbon atom of the AA. Consequently the use of enantiomerically pure AA in these syntheses enables optically active FAA to be obtained.

1. Replacement of hydrogen by fluorine

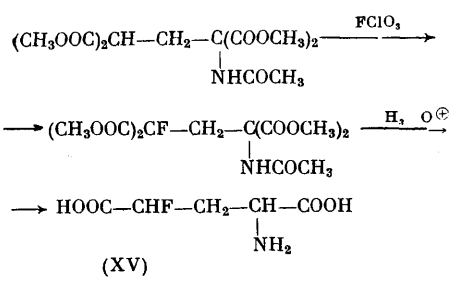
The use of methods for the direct fluorination of organic compounds to obtain aliphatic FAA is represented in the literature by only a few examples. This is evidently linked with the fact that aliphatic AA molecules are far less stable than aromatic AA towards the action of fluorine or its equivalents and also with the large quantity of reactive C–H bonds which is the reason for the very low regioselectivity of these processes. Thus after treatment of a solution of *L*-lysine in liquid HF with trifluoromethyl hypofluorite *L*-4-fluorolysine (CXIII) was isolated in low yield by ion exchange chromatography from the mixture of products. Compound (CXIII) has been used in a synthesis of a cyclic hexapeptide analogue of somatostatin.[101]



(CXIII) (LXXXV)

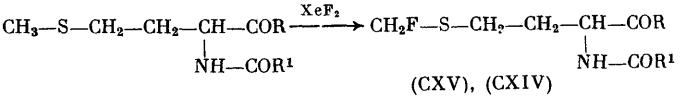
There are data on the formation of 5-fluoroisoleucine (LXXXV) by fluorinating isoleucine with trifluoromethyl hypofluorite. However its isolation was unsuccessful due to the ready heterocyclisation into 3-methylproline.[102]

4-Fluoroglutamic acid (XV) was obtained by replacing a hydrogen atom in the γ-position of tetramethyl 2-acetamido-2,4-dicarboxylglutarate with fluorine by reaction with perchloryl fluoride with subsequent hydrolysis and decarboxylation.[103–105]



(XV)

The differences in reactivity of the C–H bonds of methionine enabled the development of a preparative method for the monofluoro derivative of methionine (CXIV) and of the dipeptide methionyl-glycine (CXV) using XeF_2 as fluorinating agent.[106] It must be recorded that no products of more extensive fluorination, di- and trisubstituted compounds, were detected.

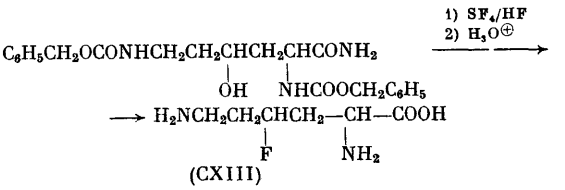


(CXV), (CXIV)

R = OCH_3, R^1 = CF_3 (CXIV); R = $NHCH_2COOC_2H_5$, R^1 = $OCH_2C_6H_5$ (CXV).

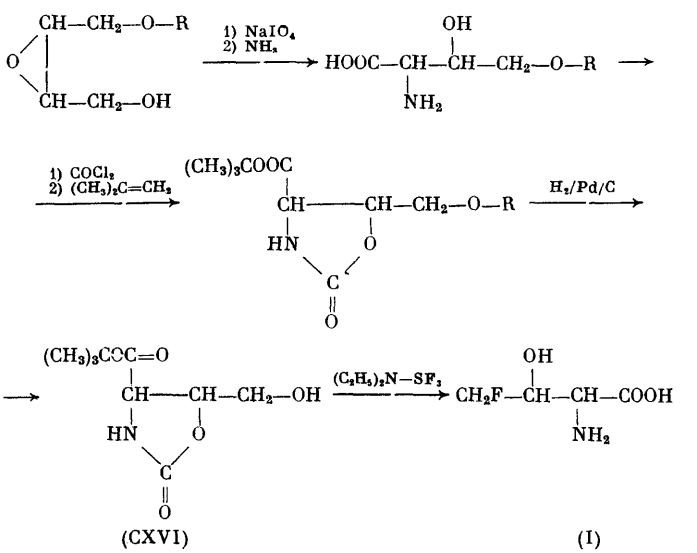
2. Replacement of a hydroxyl group by fluorine

The fluorodehydroxylation of protected 4-hydroxylysine by sulphur tetrafluoride in liquid HF proved to be a more efficient method of obtaining 4-fluorolysine (CXIII) than the direct fluorination of lysine with trifluoromethyl hypofluorite discussed above.[101]



(CXIII)

Optically pure (2*S*,3*S*)-4-fluorothreonine (I) is synthesised by the replacement of an OH group by fluorine by the reaction of diethylaminosulphur trifluoride (DAST) and the (4*S*,5*S*)-oxazolone (CXVI), which was obtained from (2*S*,3*R*)-3-benzyloxymethyl-2-hydroxymethyloxirane.[92]

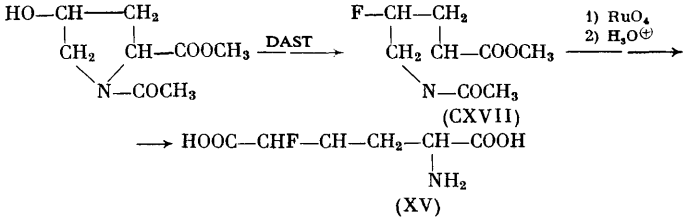


(CXVI) (I)

R = $CH_2C_6H_5$

The possibility of converting hydroxyproline into glutamic acid was used recently for the synthesis of optically pure (2*S*,4*S*)-4-fluoroglutamic acid (XV).[107] The fluorodehydroxylation of (–)-*N*-acetyl-*trans*-4-hydroxy-(*S*)-proline methyl ester by the action of DAST proceeds stereoselectively with the formation of a derivative of optically active 4-fluoroproline (CXVII). Compound

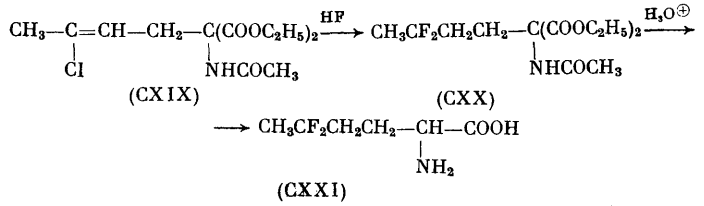
(CXVII) is oxidised regioselectively at the C(5) methylene group of the pyrrolidine ring and subsequent hydrolysis of the lactam (CXVIII) gives (2*S*,4*S*)-4-fluoroglutamic acid (XV).



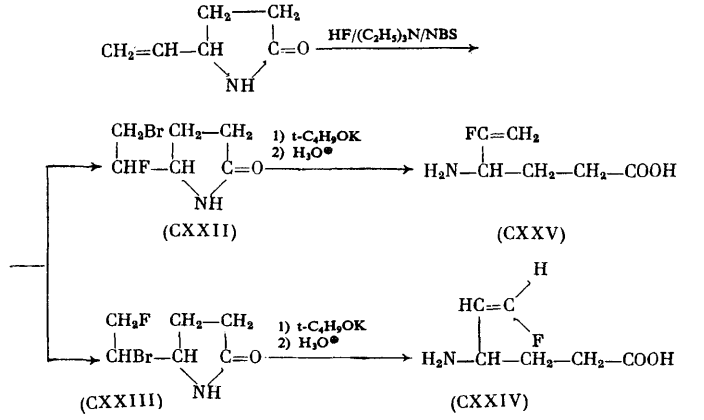
In view of the ease of *cis,trans*-isomerism of the 4-hydroxyprolines and the reduced cost of (+)-*cis*-4-hydroxy-*R*-proline it may be suggested that this method will be convenient for obtaining all four stereoisomers of 4-fluoroglutamic acid (XV).

3. Application of other methods of organofluorine chemistry to the synthesis of FAA

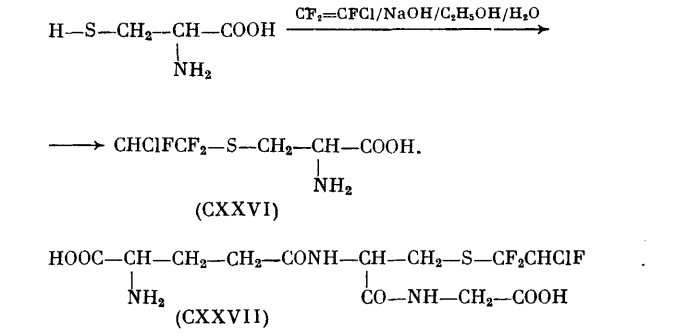
The action of hydrogen fluoride on the acetamidomalonic ester derivative (CXIX) leads to simultaneous addition of hydrogen fluoride to the C=C bond and replacement of the chlorine atom by fluorine. After hydrolysis of the product (CXX) a 50% yield of 5,5-difluoronorleucine (CXXI) is obtained.[108]



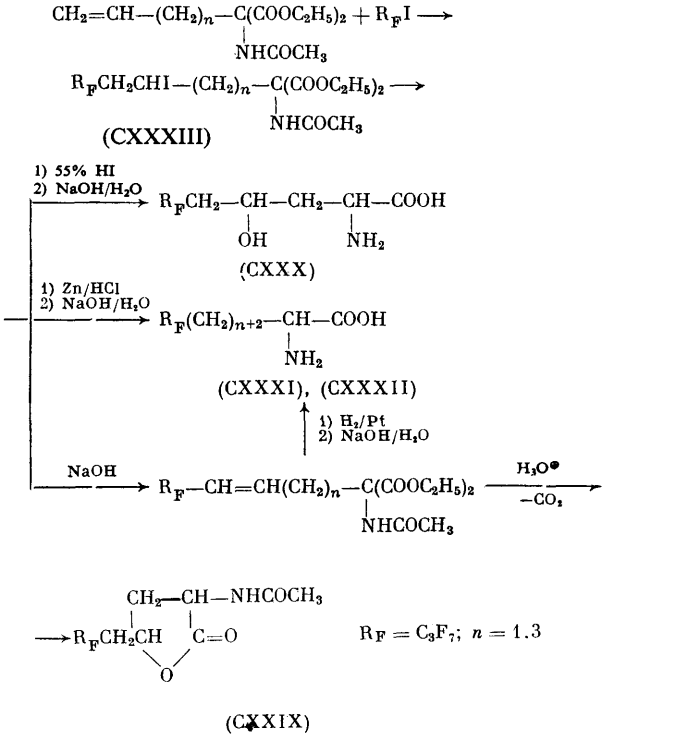
The combined addition of fluorine and bromine atoms to 5-vinylpyrrolid-2-one gives a mixture of the isomeric 5-(bromofluoroethyl)pyrrolidones (CXXIII), which is readily separated by chromatography. Dehydrobromination of compounds (CXXII) and (CXXIII) and subsequent hydrolysis leads to the formation of the γ-amino-γ-fluorovinylbutyric acids (CXXIV) and (CXXV). (*Z*)-γ-amino-γ-(2-fluoroethenyl)butyric acid (CXXIV) proved to be the strongest inhibitor of γ-aminobutyric acid (GABA) transaminase of the series of γ-fluorovinyl-substituted GABA (LXVI), (LXXVII), (CXXIV) and (CXXV).[71]



The direct chlorotrifluoroethylation of cysteine is effected by the reaction of chlorotrifluoroethylene and the disodium salt of *N*-t-butyloxycarbonyl-(*S*)-cysteine at 25 °C in aqueous ethanol.[109] (*S*)-*S*-Chlorotrifluoroethylcysteine (CXXVI) may be obtained by this reaction and from unsubstituted cysteine. The regioselectivity of the chlorotrifluoroethylation of the RS^- anion in the presence of RNH^- enables use of this approach for the direct chlorotrifluoroethylation of glutathione. The fluorinated analogues of cysteine (CXXVI) and of glutathione (CXXVII) proved to be nephrotoxic.



Progress in the area of free radical addition of perfluoroalkyl iodides to alkenic acids with a terminal C=C bond[110] has enabled development of a general method of synthesis of long chain FAA containing perfluoroalkyl groups.[111] The addition of perfluoropropyl iodide to diethyl 2-acetamido-2-allylmalonate ester or to diethyl 2-acetamido-2-(pent-4-enyl)malonate in the presence of the initiator azo-bis(isobutyronitrile) gives the products (CXXXVIII) in high yield.

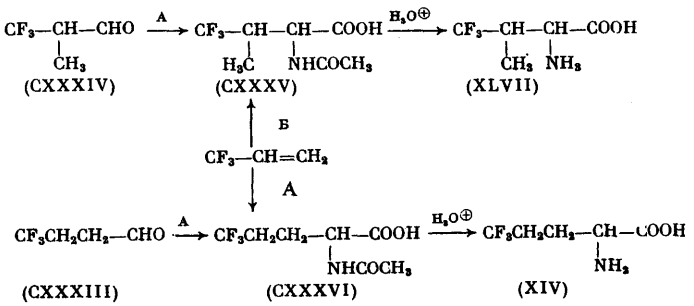


Subsequent hydrolysis of the acetamidomalonate (CXXVIII, $n = 1$) with 55% HI proceeds with simultaneous replacement of the iodine atom by hydroxyl, probably through the lactone (CXXIX), forming 2-amino-6,6,7,7,8,8,8-heptafluoro-4-hydroxyoctanoic acid (CXXX). In order to obtain free 2-amino-6,6,7,7,8,8,8-heptafluorooctanoic (CXXXI) and 2-amino-8,8,9,9,10,10,10-heptafluorodecanoic acids (CXXXII) the iodine atom is replaced by hydrogen, either directly in compound (CXXVIII) by the action of zinc and hydrochloric acid or by a two-stage process of dehydroiodination and catalytic hydrogenation, with subsequent removal of protecting groups and decarboxylation of one carboxyl group. This method is distinguished by high yields at each stage and by the availability of the starting materials. The FAA (CXXXI) and (CXXXII) may also be obtained from the corresponding α-bromocarboxylic acids.[111]

IV. Special methods of obtaining fluorine-containing amino acids

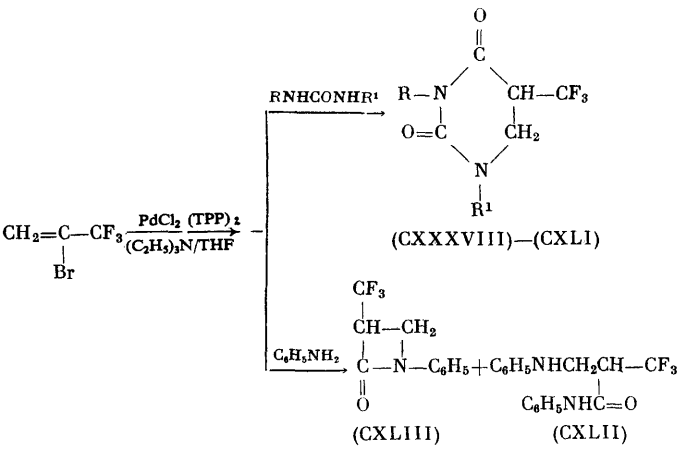
1. Amidocarbonylation of fluorine-containing amino acids

Trifluorovaline (XLVII) and trifluoronorvaline (XIV) are obtained by the amidocarbonylation of 4,4,4-trifluorobutyric (CXXXIII) and 3,3,3-trifluoroisobutyric (CXXXIV) aldehydes respectively. The amidocarbonylation of aldehydes (CXXXIII) and (CXXXIV) with acetamide in the presence of cobalt carbonyl and a mixture of carbon monoxide and hydrogen is carried under a pressure of about 100 atm on heating to 120 °C. Hydrolysis of the acetamides (CXXXV) and (CXXXVI) formed in high yield gives the free FAA (XLVII) and (XIV).[48,50,112] The trifluorovaline formed in this way is a mixture of two diastereoisomers in a ratio 38 : 62. Since the synthesis of the aldehyde (CXXXIII) from 3,3,3-trifluoropropene requires the same catalyst, viz. $Co_2(CO)_8$ and a CO/H_2 mixture,[47,113] the process of making trifluoronorvaline (XIV) in 94% purity may be effected directly from 3,3,3-trifluoropropene through the step of forming aldehyde (CXXXIII) *in situ*. Addition of small quantities of rhodium carbonyl to $Co_2(CO)_8$ leads to a change in the regioselectivity of the reaction giving *N*-acetyl-3,3,3-trifluorovaline (CXXXV) as the main reaction product (96% pure). Thus the regioselectivity of the preparation of trifluorovaline (CXXXV) or trifluoronorvaline (XIV) from trifluoropropene through the two steps of hydroformylation and amidocarbonylation is determined only by the nature of the catalyst.[114–116] The FAA (XLVII) and (XIV) are obtained in pure form by crystallisation of the crude product. Racemic trifluoronorvaline (XIV) has been separated into its (*S*)- and (*R*)-enantiomers by enzymic hydrolysis of its *N*-acetyl derivative.[50]



A = CO, H_2, CH_3CONH_2, $Co(CO)_8$; B = A + $Rh_6(CO)_{16}$.

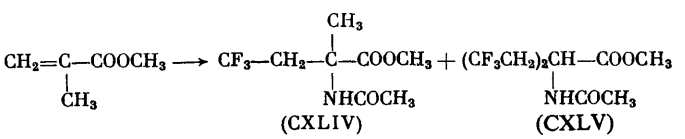
3,3,3-Trifluoropropene also proved to be a convenient starting material for the synthesis of α-trifluoromethyl-β-alanine derivatives. Trifluoropropene is converted in two stages (bromination, dehydrobromination) into 2-bromo-3,3,3-trifluoropropene (CXXXVII) in high yield.[117] Ureidocarbonylation of the propene (CXXXVII) with 1,3-dimethylurea and carbon monoxide on a catalyst consisting of the complex of palladium chloride with triphenylphosphine leads to the formation of 5-trifluoro-1,3-dimethyl-5,6-dihydrouracil (CXXXVIII) in 70% yield. The use of methylurea in this reaction gives a mixture of the 1-methyl- (CXXXIX) and 3-methyl-substituted (CXL) dihydrouracils in a ratio of 1 : 5. Unsubstituted urea forms 5-trifluormethyldihydrouracil (CXLI) (26%),[48,118,119] from which it is possible to obtain free α-trifluoromethyl-β-alanine (LXXVII) by hydrolysis. The use of aniline instead of urea enables the amide (CXLII) and β-lactam (CXLIII) of *N*-phenyl-α-trifluoromethyl-β-alanine to be obtained.[48]



TPP = $(C_6H_5)_3P$; R = R^1 = CH_3 (CXXXVIII); R = CH_3, R^1 = H (CXXXIX); R = H, R^1 = CH_3 (CXL); R = R^1 = H (CXLI)

2. The trifluoromethyl-acetamidation of olefins

The electrolysis of a mixture of trifluoroacetic acid and methyl methacrylate in aqueous acetonitrile leads to the formation of a complex mixture of products. From this the methyl esters of β-trifluoromethyl-α-methylalanine (CXLIV) and bis(trifluoroethyl)-glycine (CXLV) are isolated in 20 and 5% yield respectively.[120] As suggested, the electrochemical trifluoromethyl-acetamidation of methyl methacrylate may be used for the preparation of FAA (CXLIV).



At present the synthesis of fluorine-containing amino acids is a component of the approach to the solution of one of the basic problems of bio-organic chemistry, namely the purpose-directed modification of the natural bioregulators (mainly peptidic in nature)

to adjust their functions and properties (activities) in the required direction. Amino acids with one or more fluorine atoms on their carbon skeleton are required for the solution of this problem. As is seen from the literature data considered in this review the known methods of synthesis of aliphatic FAA enable practically any AA containing one fluorine atom or perfluoroalkyl groups to be obtained. However, the methods cited in the present review are not all of preparative value. Fluorine-containing amino acids, including the aliphatic AA, still remain difficultly accessible compounds, paticularly as pure diastereo- and/or enantiomers, for the majority of biochemical laboratories. The problem of the asymmetric synthesis of FAA must be taken separately and with certain exceptions has no optimal solution at present. Consequently it must be expected that further work in the area of FAA synthesis will be directed mainly to the creation of preparative methods of synthesis of these compounds from available organofluorine compounds using the latest achievements of organometallic chemistry, engineered enzymology and asymmetric synthesis.

References

1. M Sanada, T Mijano, S Iwadare, et al. *J. Antibiotics,* 1986, **39** 259
2. S Hunt *Chemistry and Biochemistry of Amino Acids* (Edited by G C Barrett), Chapman and Hall Ltd., London, 1985, p. 55
3. A D Argoudelis, R R Herr, D J Mason, et al. *Biochemistry,* 1967, **6** 165; *Chem. Abs.*, 1967, **66** 35 546x
4. T Shiba, Y Mukunoki, H Akiyama *Tetrahedron Lett.*, 1974, 3085
5. A H Hunt, M Debono, K E Merkel, et al. *J. Org. Chem.*, 1984, **49** 635
6. D H Williams *Acc. Chem. Res.*, 1984, **17** 364
7. S K Chung, S L Heald, P W Jeffs *J. Org. Chem.*, 1987, **52** 1606
8. N Ishikawa *Progress in the Technology of Fluorine Compounds* (N Ishikawa, Editor) (Translated into Russian), Mir, Moscow, 1984, p. 18
9. R Filler *J. Fluorine Chem.*, 1986, **33** 3
10. M Sieler, M J Jung, J Koch-Waser *Enzyme-activated Irreversible Inhibitors,* Elsevier, Amsterdam, 1978, p. 396
11. C Walsh *Tetrahedron,* 1982, **38** 871
12. J Kollonitsch *Isr. J. Chem.*, 1978, **17** 53
13. J Kollonitsch *Biomedicinal Aspects of Fluorine Chemistry* (Edited by R Filler et al.), Kodansha Ltd., Elsevier Biomedical Press, Tokyo–Amsterdam, 1982, p. 93
14. E Kobayashi, N Kumagane, T Taguti *Progress in the Technology of Fluorine Compounds*) (N Ishikawa, Editor) (Translated into Russian), Mir, Moscow, 1984, p. 526
15. J T Welch *Tetrahedron,* 1987, **43** 3123
16. M J Jung *Bioorganic Chem.*, 1986, **14** 429
17. N Ishikawa (Editor) *Fluorine Compounds: Synthesis and Applications* (Translated into Russian), Mir, Moscow, 1990
18. J T Gorig *Biomedicinal Aspects of Fluorine Chemistry* (Edited by R Filler et al.), Kodansha Ltd., Elsevier Biomedical Press, Tokyo–Amsterdam, 1982, p. 163
19. A Dahbi, S Hamman, C Beguin *J. Fluorine Chem.*, 1985, **29** 185
20. H Hagino, K Nakayama *Agric. Biol. Chem.*, 1975, **39** 331
21. H Hagino, K Nakayama *Agric. Biol. Chem.*, 1975, **39** 343
22. E Kobayashi, I Kumagane, T Taguti *Progress in the Technology of Fluorine Compounds*) (N Ishikawa, Editor) (Translated into Russian), Mir, Moscow, 1984, p. 494
23. E S Garnett, G Firnau, C Nahmias *Nature (London)*, 1983, **305** 137
24. D F Loncrini, R Filler *Adv. Fluorine Chem.*, 1970, **6** 43
25. F Weygand, V Otmeyer *Usp. Khim.*, 1970, **39**(4) 622 [English Translation in *Russ. Chem. Rev.*, 1970(4)]
26. V P Kukhar', Yu L Yagupol'skii, V A Soloshonok *Usp. Khim.*, 1990, **59**(1) 149 [English Translation in *Russ. Chem. Rev.*, 1990(1)]
27. L M Yagupol'skii *Aromaticheskie i Geterotsiklcheskie Soedineniya s Ftorsoderzhashchimi Zamestitelyami* (Aromatic and Heterocyclic Compounds with Fluorine-Containing Substituents), Nauk. Dumka, Kiev, 1988, p. 229
28. H M Walborsky, M Baum, D F Loncrini *J. Am. Chem. Soc.*, 1955, **77** 3637
29. US P. 2 662 915; *Chem. Abs.*, 1954, **48** 12 795b
30. M S Raasch *J. Org. Chem.*, 1958, **23** 1567
31. M Hidlicky, B Kakac *Collect. Czech. Chem. Commun.*, 1966, **31** 110; *Chem. Abs.*, 1966, **64** 19 757c
32. Czechoslovak P. 123 002; Chem. Abs., 1968, **69** 26 783o
33. V Tolman, K Veres *Tetrahedron Lett.*, 1964, 1967; *Chem. Abs.*, 1964, **61** 10 771b
34. W Steglich, H U Heininger, H Dworschank, et al. *Angew. Chem.*, 1967, **6** 822
35. T Tsushima, K Kawada, S Ishihara, et al. *Tetrahedron,* 1988, **44** 5375
36. M Hudlicky *Tetrahedron Lett.*, 1960, 21; *Chem. Abs.*, 1960, **54**, 24 382e
37. Czechoslovak P. 99 613; *Chem. Abs.*, 1962, **56** 12 745c
38. R L Buchanan, F H Dean, F L M Pattison *Can. J. Chem.*, 1962, **40** 1571; *Chem. Abs.*, 1962, **57** 11 005i
39. B M Trost, H C Arndt, P E Srege, et al. *Tetrahedron Lett.*, 1976, 3477
40. T Koizumi, T Hagi, Y Horio, et al. *Chem. Pharm. Bull.*, 1987, **35** 3959
41. T Taguchi, G Tomizawa, M Nakajima, et al. *Chem. Pharm. Bull.*, 1985, **33** 4077
42. V P Kukhar', V A Soloshonok, Yu N Belokon', et al. *Vsesoyuz. Seminar po Khimii Fiziologicheski Aktivnykh Soedinenii: Tez. Dokl.* (All-Union Seminar on the Chemistry of Physiologically Active Compounds: Abstracts of Reports), Chernogolovka, 1989, p. 145
43. Yu M Belokon', N I Chernoglazova, K A Kochetkov, et al., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 804
44. Yu N Belokon', A G Bulychev, S V Vitt, et al. *J. Am. Chem. Soc.*, 1985, **107** 4252
45. U Schöllkopf, R Meyer *Liebigs Ann. Chem.*, 1981, 1469
46. A L Castelhano, S Horne, R Billedeau, et al. *Tetrahedron Lett.*, 1986, 2435
47. US P. 4 370 504; *Ref. Zh. Khim.*, 1983, 24N148P
48. I Ojima *L'Actualite Chemi,* France, 1987, p. 171
49. I Ojima, K Kato *ACS, IX Winter Fluorine Conference*, 1989, p. 29
50. I Ojima, K Kato, K Nakahashi, et al. *J. Org. Chem.*, 1989, **54** 4511
51. V A Soloshonok, V S Brovarets, Yu L Yagupol'skii *Zh. Org. Khim.*, 1987, **23** 2350
52. V S Brovarets, O P Lobanov, A A Kiselenko, et al. *Zh. Obshch. Khim.*, 1986, **56** 1492

53. E M Rokhlin, N P Gambaryan, T Y Chen, et al. *Dokl. Akad. Nauk SSSR*, 1960, **134** 1367
54. R L Dannley, R G Taborsky *J. Org. Chem.*, 1957, **22** 1275
55. W A Zygmunt, P A Tavormina *Can. J. Microbiol.*, 1966, **12** 143; *Chem. Abs.*, 1966, **63** 11 569f
56. J A Stekol *Transmethylation Methionine Biosyn.*, 1965, 231; *Chem. Abs.*, 1966, **64** 18 229d
57. N Muller *J. Fluorine Chem.*, 1987, **36** 163
58. K Weinges, E Kromm *Liebigs Ann. Chem.*, 1985, 90
59. H Gershon, L Shanks *J. Pharm. Sci.*, 1978, **67** 715
60. D Butina, M Hudlicky *VI Europ. Symp. Fluor. Chem.*, 1977, p. 30
61. F Heinzer, P Martin *Helv. Chim. Acta*, 1981, **64** 1379
62. H M Walborsky, M E Baum *J. Org. Chem.*, 1956, **21** 538
63. D F Loncrini, H M Walborsky *J. Med. Chem.*, 1964, **7** 369; *Chem. Abs.*, 1964, **61** 4204
64. J Lazar, W A Sheppard *J. Med. Chem.*, 1968, **11** 138; *Chem. Abs.*, 1968, **68** 78 588w
65. H Lettre, U Wolcke *Liebigs Ann. Chem.*, 1967, 75
66. Y Maki, K Inukai *J. Synth. Org. Chem. Jpn.*, 1976, **34** 722; *Ref. Zh. Khim.*, 1977, 11E106
67. M Hirosige, U Akio *VII Europ. Fluor. Chem.*, 1980, p. 33
68. B Cavalleri, E Bellasio, E Testa *Gazz. Chem. Ital.*, 1966, **96** 253; *Chem. Abs.*, 1966, **65** 3735c
69. H M Walborsky, M Schwarz *J. Am. Chem. Soc.*, 1953, **75** 3241
70. I A McDonald, M G Palfreyman, M Jung, et al. *Tetrahedron Lett.*, 1985, 4091
71. M Kolb, J Barth, J-G Heydt, et al. *J. Med. Chem.*, 1987, **30** 267
72. I L Knunyants, Yu A Cheburkov *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1960, 2162
73. W H Vine, K Hsieh, G R Marshall *J. Med. Chem.*, 1981, **24** 1043; *Ref. Zh. Khim.*, 1982, 9E123
74. W H Vine, D A Bruechner, P Needleman, et al. *Biochemistry*, 1973, **12** 1630; *Chem. Abs.*, 1973, **79** 488w
75. A V Eremeev, I V Solodin, F R Polyak *Izv. Akad. Nauk Latvian SSR, Ser. Khim.*, 1985, 345
76. I V Solodin, A V Eremeev, I I Chervin, et al. *Khim. Geterotsikl. Soedin.*, 1985, 1359
77. A V Eremeev, I V Solodin, E E Liepin'sh *Khim. Geterotsikl. Soedin.*, 1984, 917
78. I V Solodin, F D Polyak, A V Eremeev, et al. *Khim. Geterotsikl. Soedin.*, 1985, 1335
79. I V Solodin, A V Eremeev, E E Liepin'sh *Khim Geterotsikl. Soedin.*, 1985, 505
80. T Y Chen, N P Gambaryan, I L Knunyants *Dokl. Akad. Nauk SSSR*, 1960, **133** 1113
81. T Fuchikami, A Yamanouchi, I Ojima *Synthesis*, 1984, 766
82. Japanese P. 45/81 452; *Ref. Zh. Khim.*, 1986, 230 116P
83. T Kitszume, K Murata *J. Fluorine Chem.*, 1987, **36** 339
84. I M Zalesskaya, A N Blakitnyi, E P Saenko, et al. *Zh. Org. Khim.*, 1980, **16** 1194
85. M Hudlicky *II Europ. Fluorsymposium*, 1968, p. 164
86. E A Hallinan, J Fried *Tetrahedon Lett.*, 1984, 2301
87. H Umezawa, T Aoyagi, H Morishima, et al. *J. Antibiotics*, 1970, **23** 259 *Chem. Abs.*, 1970, **73** 581 423r
88. S Thaisrivong, D T Pals, W M Kati, et al. *J. Med. Chem.*, 1985, **28** 1555
89. S Thaisrivong, D T Pals, W M Kati, et al. *J. Med. Chem.*, 1986, **29** 2080
90. G Guanti, L Banfi, E Narisano *Tetrahedron*, 1988, 5553
91. H M Walborsky, M E Baum *J. Am. Chem. Soc.*, 1958, **80** 187
92. C Scolastico, E Conca, L Prati, et al. *Synthesis*, 1985, 850
93. N P Gambaryan, L A Simonyan, I L Knunyants *Dokl. Akad. Nauk SSSR*, 1964, **155** 833
94. N P Gambaryan, L A Simonyan *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1964, 1529
95. R L Buchanan, P L M Pattison *Can. J. Chem.*, 1965, **43** 3466; *Ref. Zh. Khim.*, 1966, 14Zh427
96. T Tsushima, K Kawada, O Shiratori, et al. *Heterocycles*, 1985, **23** 45
97. J J McGuire, J K Coward *J. Biol. Chem.*, 1985, **260** 6747
98. US P. 4 584 375; *Ref. Zh. Khim.*, 1987, 40 147P
99. O M Rennert, H S Anker *Biochemistry*, 1963, **2** 471; *Chem. Abs.*, 1963, **58** 11 706f
100. E D Bergmann, A Sohen *Tetrahedron Lett.*, 1965, 2085
101. US P. 4 427 661; *Chem. Abs.*, 1984, **100** 192 286
102. J Kollonitsch, L Barash, G A Doldouras *J. Am. Chem. Soc.*, 1970, **92** 7494
103. V Tolman, K Veres *Tetrahedron Lett.*, 1966, 3909
104. V Tolman, K Veres *Collect. Czech. Chem. Commun.*, 1967, **32** 4460; *Chem. Abs.*, 1968, **68** 12 428n
105. L V Alekseeva, B N Lundin, N L Burde *Zh. Obshch. Khim.*, 1967, **37** 1754
106. A F Janzen, P M C Wang, A E Lemire, et al. *J. Fluorine Chem.*, 1983, **22** 557
107. M Hudlicky *ACS IX Winter Fluorine Conference*, 1989, p. 26
108. M Hudlicky *Collect. Czech. Chem. Commun.*, 1967, **32** 453; *Chem. Abs.*, 1967, **66** 55 722e
109. D R Dohn, J R Leininger, L H Lash *J. Pharmacol. Exp. Ther.*, 1985, **235** 851
110. N O Brace *J. Org. Chem.*, 1962, **27** 4491
111. N O Brace *J. Org. Chem.*, 1967, **32** 430
112. I Ojima *Chem. Rev.*, 1988, **88** 1011
113. T Fuchikami, I Ojima *J. Am. Chem. Soc.*, 1982, **104** 3527
114. I Ojima *J. Mol. Catal.*, 1986, **37** 25
115. I Ojima, K Hirai, M Fujita, et al. *J. Organomet. Chem.*, 1985, **279** 203
116. I Ojima, M Okabe, K Kato, et al. *J. Am. Chem. Soc.*, 1988, **110** 150
117. A L Henne, M Nager *J. Am. Chem. Soc.*, 1951, **73** 1042
118. T Fuchikami, I Ojima *Tetrahedron Lett.*, 1982, 4099
119. I Ojima *J. Fluorine Chem.*, 1987, **35** 31
120. K Uneyama, H Nanbu, *J. Org. Chem.*, 1988, **53** 4598