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Syntheses of fluorinated amino acids: from the classical to the modern concept

Review Article

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Summary. A survey of the synthetic pathways leading to the fluorine-containing analogues of amino acids is given. From the great number of syntheses the typical examples are selected and divided into two groups: classical syntheses and the modern ones. The classical ammonolysis of halogeno acids and equivalent reactions are discussed as first, followed by a few examples of oxo → amino group transformation. Conversion of the oxo compounds into amino acids richer by one carbon atom is realized by the Strecker and hydantoin syntheses. For the prolongation by two carbons, the Erlenmeyer azlactone method and alkylation of CH-acidic esters are applied. The modern syntheses are represented by direct fluorination by elemental fluorine and other electrophilic fluorinating reagents. Further examples include the applications of the Yarovenko reagent, sulphur tetrafluoride and its derivative DAST. The use of trifluoropyruvates as the fluoro synthons is mentioned briefly. Finally, the examples of the amidocarboxylation method and the syntheses of diverse ω-fluorinated methionines are shown.

Keywords: Amino acids – Fluoro analogues – Synthesis

Introduction

The very numerous syntheses used for the preparation of fluorinated amino acids may be – in principle – divided into two large groups: those based on the methodology of the amino acid chemistry and those making use of the chemistry of organofluorine compounds. There is no question about that in some cases it is difficult to place the exact borderline between these two groups, which, at least from the practical point of view, represent the classical and the modern concept in the fluoro amino acid synthesis.

Classical synthetic routes

This group covers methods which follow, more or less exactly, the pathways used in the chemistry of their nonfluorinated counterparts. This access, evidently not very pretentious with respect to the chemist's inventiveness, is based on two premises:

1) stability and chemical inertness of the C—F bonds;
2) similar reactivity of the fluorinated and non-fluorinated reactants.

Provided that both of these hypotheses are valid, this concept represents a viable synthetic strategy and, as such, it was very frequently applied. However, this mechanistic point of view does not take into account the extreme electronegativity of fluorine, a fact which, in its consequences, is responsible for a limited applicability of these methods. The limitations are caused by:

1) the change of polarity of the functional groups and bonds in the vicinity of fluorine atoms;
2) lower reactivity of some fluorinated reactants, especially of the polyfluorinated ones;
3) the formerly unexpected considerable lability of the C—F bonds in the β-position and, to some extent, also in the γ-position to carbonyl.

Despite these limitations, many fluorinated amino acids have been successfully prepared by these methods. First of them appeared as early as in the 1930's.

Of the classical routes, the simplest one is the amination of a halogeno acid or ester by ammonia or its suitable equivalent. ω-Fluoro-2-amino acids were prepared by this way, generally in moderate yields (Lettré and Wölcke, 1967).

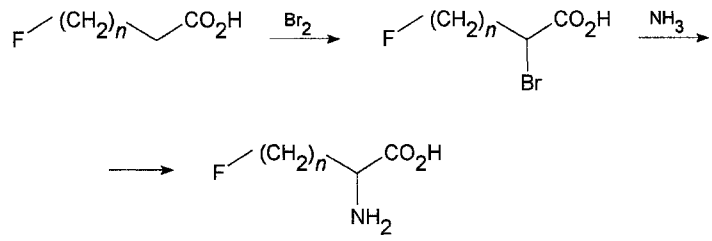

Fig. 1

This method has been also used in the preparation of 3-fluoro-2-amino acids from the corresponding alk-2-enoic acids, which were bromofluorinated and then ammonolyzed (Gershon et al., 1973).

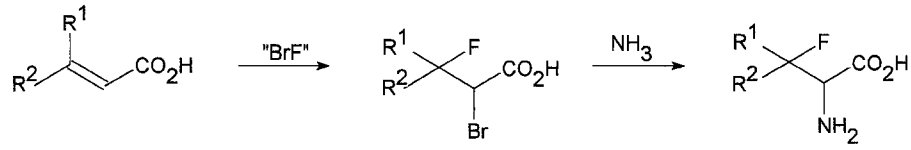

Fig. 2

Although direct ammonolysis may be applied also in the synthesis of 2-amino acids containing the polyfluoro alkyl substituent in the terminal position (Brace, 1967; Muller, 1987), problems may arise when a strongly electronegative CF_3 or, at least CF_2 group is present in the γ-position to the halogen. In these cases elimination occurs instead of substitution; according to the reaction conditions, the ensuing addition of ammonia may result in the formation of the isomeric β-amino acid. These difficulties are successfully overcome by converting the halogeno ester first into the azido derivative, which is then reduced (Walborsky and Baum, 1956; Loncrini and Walborsky, 1964; Lazar and Sheppard, 1968; Maki and Inozui, 1976; Heinzer and Martin, 1981).

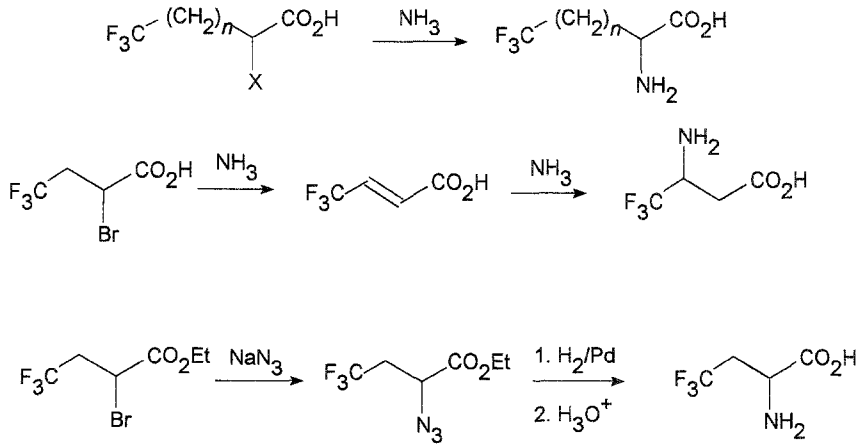

Fig. 3

The same pathway was used in the synhesis of a 4,4-difluoro-2-amino acid (Tolman and Sedmera, to be published).

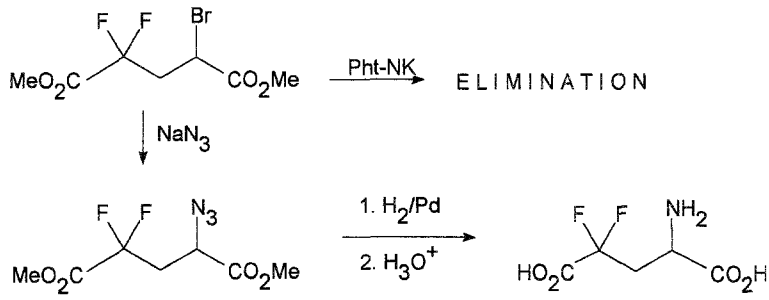

Fig. 4

The azido route is generally applicable and has been used even in the case of sensitive compounds. Some disadvantage of this access is that the liquid azido esters are often difficult to purify. On the other hand, amination using potassium phthalimide, when applicable, yields mostly crystalline intermedi-

ates. It has been applied, for example, in the syntheses of polyfunctional fluoro amino acids (Cavalleri et al., 1966a, 1966b; Hanuš et al., 1973; Tolman and Vereš, 1967; Tolman and Beneš, 1976).

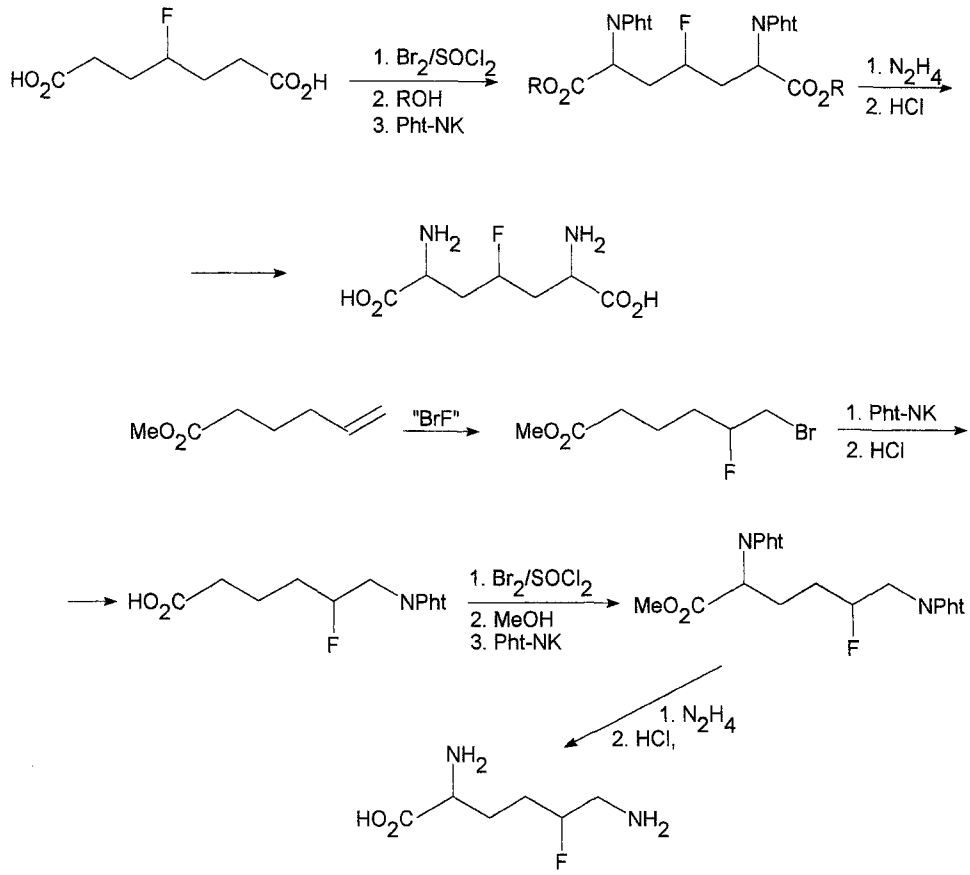

Fig. 5

Ammonolysis of the oxirane ring, which is an another variant of amination, may occur in both directions, as demonstrated by the syntheses of 4-fluorophenylisoserine (Blažević and Zymalkowski, 1975; Kamandi et al., 1975) and 4,4,4-trifluorothreonine (Walborsky and Baum, 1958).

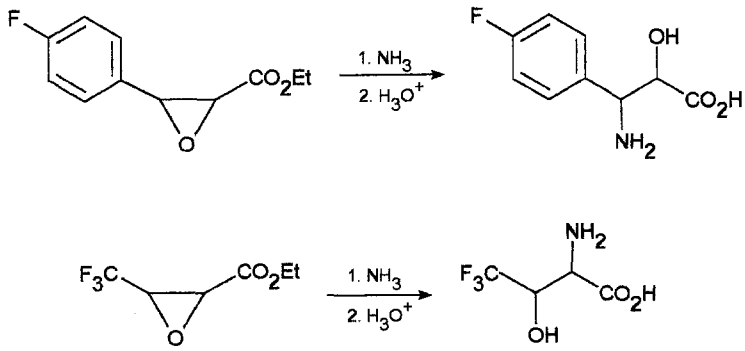

Fig. 6

2-Oxo acids may be converted into the corresponding 2-amino acids either directly, i.e. by reductive amination, or by reduction of their nitrogen derivatives, such as oximes or phenylhydrazones. The reductive amination was elaborated, for instance, for the synthesis of deuterated 3-fluoro-2-alanine, the (R)-antipode of which is the broad-spectrum antimicrobial Fludalanin (Dolling et al., 1978). *Erythro*-3-fluoro-3-phenyl-2-alanine was prepared analogously from 3-fluoro-3-phenylpyruvic acid. Two reagents were compared, from which the sodium borohydride/ammonia system was much more effective (Tsushima et al., 1980, 1984).

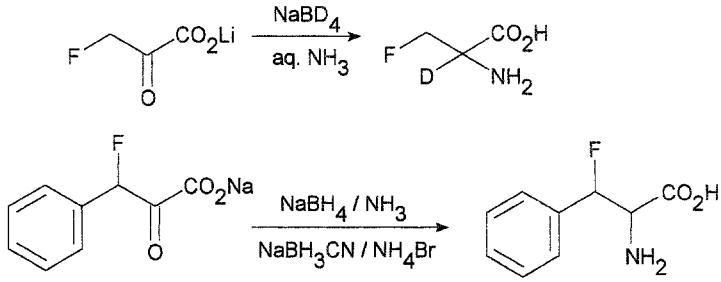

Fig. 7

The oxime reduction may be demonstrated by the synthesis of 5,5,5-trifluoroleucine from ethyl 3-trifluoromethylbutenoate (Rennert and Anker, 1963). Similarly, 4,4,4-trifluorothreonine was prepared by hydrogenolysis of a phenylhydrazone intermediate (Walborsky and Baum, 1958).

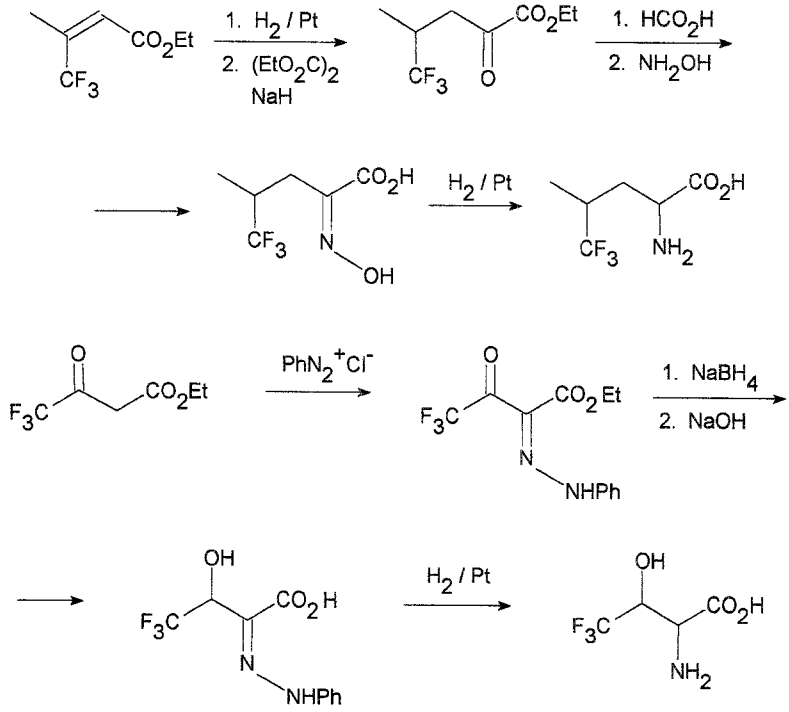

Fig. 8

The transformation of oxo compounds into 2-amino acids richer by one carbon atom is realized by well-known Strecker and hydantoin syntheses. Although both reactions are routinelly applied in the classical syntheses of non-fluorinated amino acids, their use in the preparation of the fluoro analogues is rather scarce.

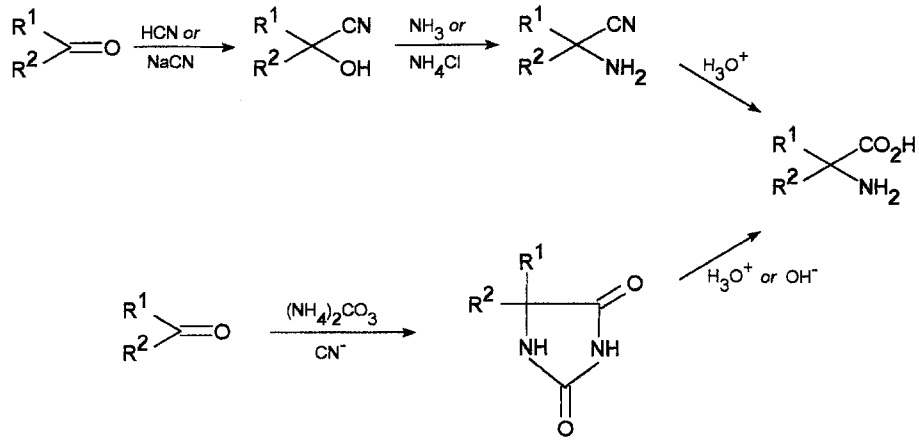

Fig. 9

The Strecker route has been employed, among others, in the synthesis of amino acids with terminal CF_3-group, the trifluoro derivatives of 2-aminoisobutyric acid (Christensen and Oxender, 1963), norvaline (Walborsky et al., 1955) and isoleucine (Muller, 1987). The syntheses proceed according to the general scheme of the Strecker synthesis and do not need more commentary. It should be noted that 4,4,4-trifluorobutanal was converted into 5,5,5-trifluoronorvaline also by the hydantoin synthesis in a substantially higher yield than under the Strecker conditions (Walborsky et al., 1955).

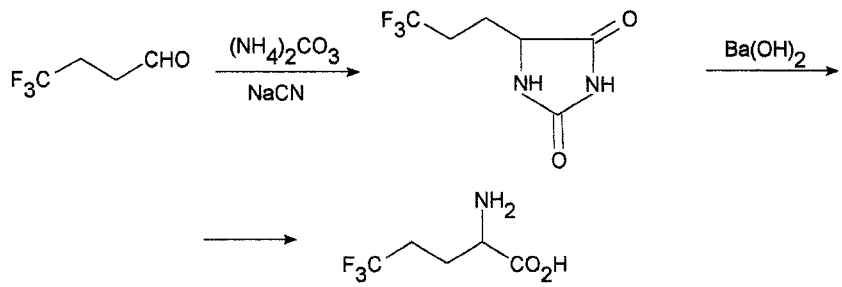

Fig. 10

Other examples of the use of hydantoin synthesis are the conversions of methyl 5-bromolevulinate into 2-fluoromethylglutamic acid (Kuo and Rando, 1981) and of 5,5,5-trifluoro-4-thiapentanal into 6,6,6-trifluoromethionine (Dannley and Taborsky, 1957).

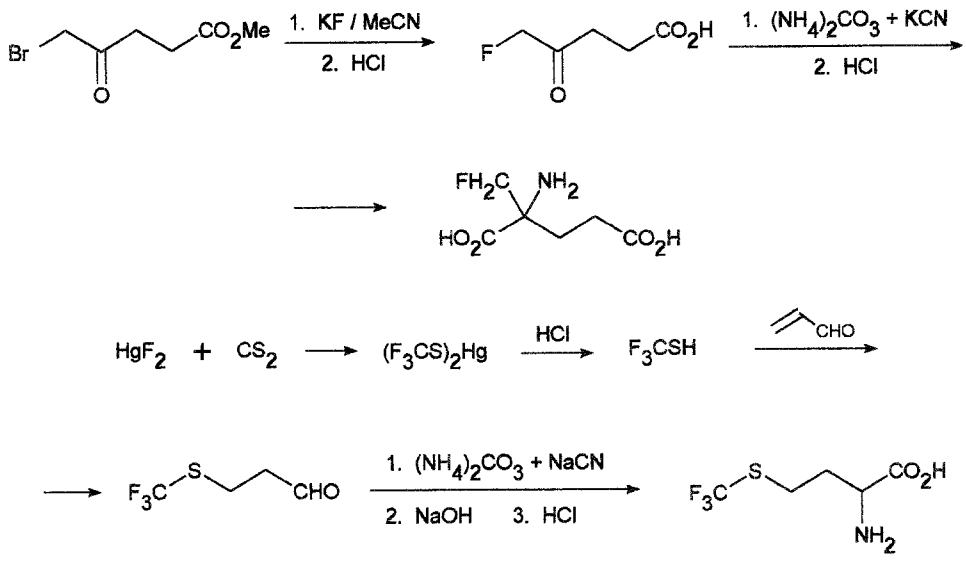

Fig. 11

While amination methods give amino acids with the same number of carbon atoms as in the starting compound, and Strecker and hydantoin syntheses result in chain prolongation by one carbon atom, amino acids richer by two carbons are prepared by Erlenmeyer azlactone synthesis and by the alkylation of CH-acidic esters. The Erlenmeyer synthesis, shown on Fig. 12, has been widely exploited in the preparation of many fluorine-containing analogues of aromatic amino acids.

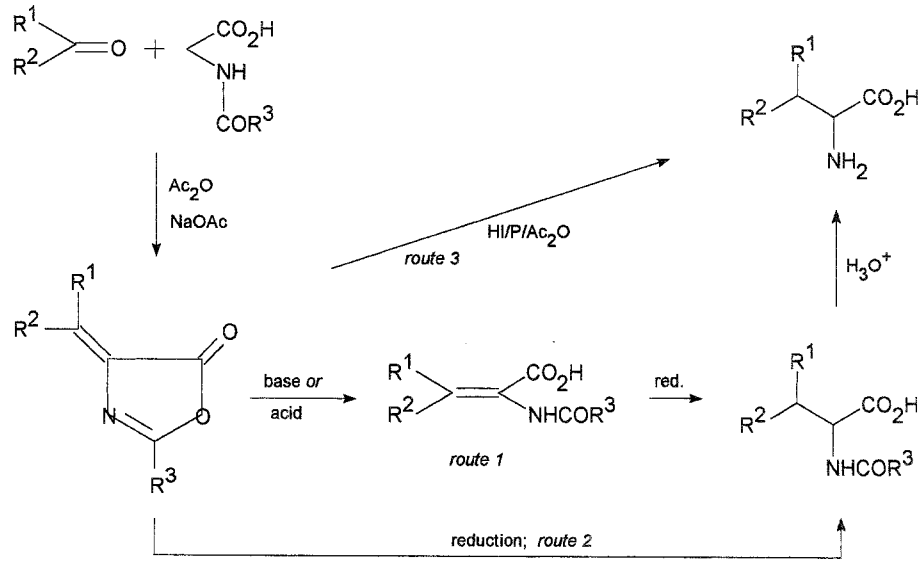

Fig. 12

Ring-fluorinated phenylalanines, synthesized by the azlactone method, were among the first fluoro amino acids ever prepared. All three monofluorophenylalanines were reported as early as in 1932 (Schiemann and Roselius, 1932; Schiemann and Winkelmüller, 1932; Bennett and Niemann, 1950). Condensations of N-acetyl or N-benzoylglycine with fluorinated benzaldehydes or acetophenones led to 2,4-disubstituted 5-oxazolones, which were converted into the desired fluoro amino acids by a combination of reduction and hydrolysis. Besides the monofluorophenylalanines, many polyfluorinated phenylalanine analogues, having from two to five fluorine atoms on the ring (Shishkin and Mamaev, 1965, 1966; Filler et al., 1969; Prudchenko, 1970) and all three isomeric trifluoromethylphenylalanines (Filler and Novar, 1960) were prepared by this method.

It is worth of note that the presence of a polyfluorinated substituent in the azlactone facilitates the hydrolytic step; azlactones derived from the trifluoromethylbenzaldehydes (Filler and Novar, 1960), 3-(pentafluorophenyl) propanal and 3-formyl-4,5,6,7-tetrafluoroindole (Ojima et al., 1989) are easily cleaved by simple alcoholysis or by aqueous acetone.

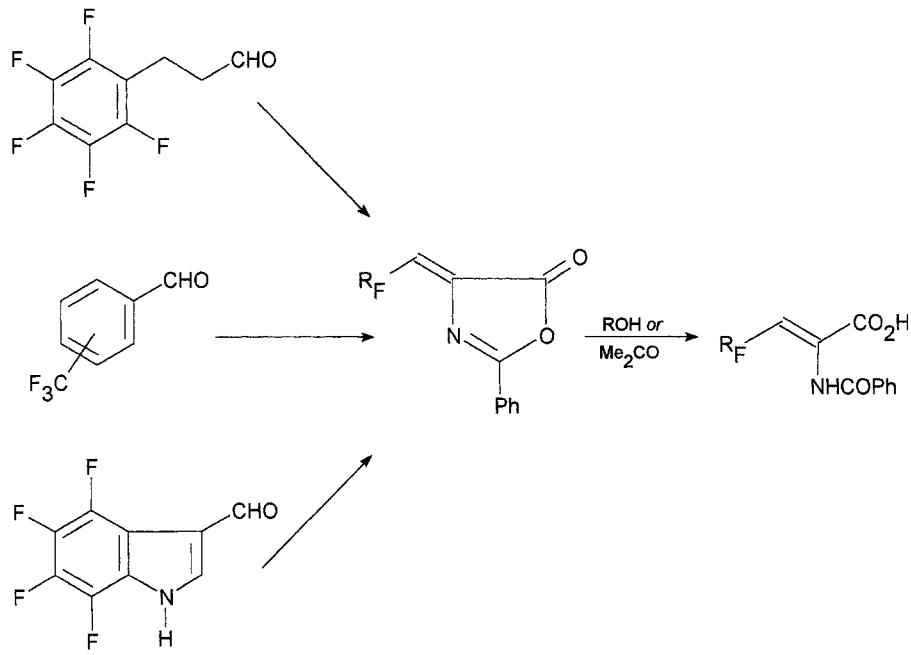

Fig. 13

In the past decade the azlactone synthesis has been extended also into the aliphatic series. It has been found that the azlactone formation from aliphatic fluoro aldehydes and N-benzoylglycine is effectively catalyzed by the lead(II) and zinc acetates, instead of the sodium salt used in the original Erlenmeyer version (Sagami 1981a, 1981b; Ojima et al., 1989). 5,5,5-Trifluoroleucine and 6,6,6-trifluoronorleucine were thus prepared from the appropriate trifluorobutanals in very good yields.

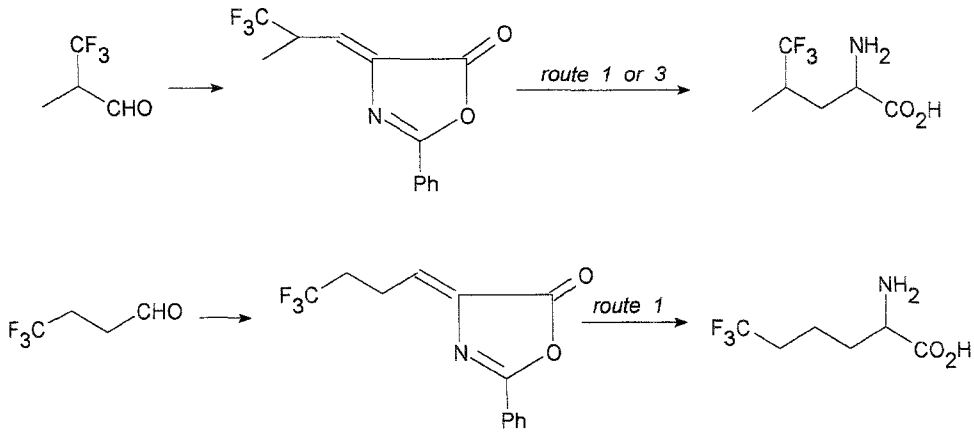

Fig. 14

The conversion of fluorinated synthons into 2-amino acids with 2 more carbon atoms is routinelly realized also through the alkylation of diverse CH-acidic esters. More types of the CH-acidic compounds were employed, the most favoured among them being the esters of acetamidomalonic acid. Three homologous ω-fluoro amino acids were prepared by this pathway (Lontz and Raasch, 1953; Raasch, 1958), the second step of which was complicated by unexpected problems. To avoid loss of fluorine, hydrolysis must be effected under mild conditions; even so, yields were only moderate.

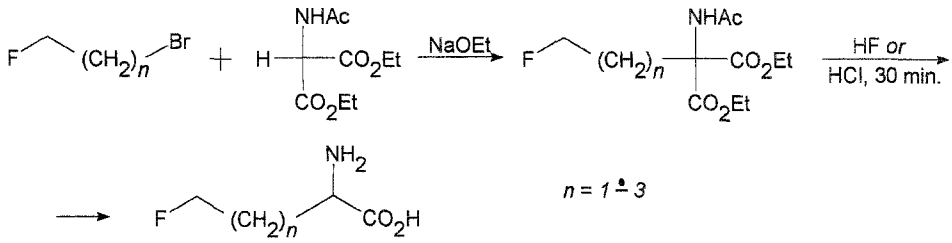

Fig. 15

In contrast to the monofluoro compounds, amino acids containing the trifluoromethyl group are stable under acidic hydrolysis; on the other hand, the presence of this group in the alkylating agent decreases its reactivity. Strong electrophiles such as the O-triflates must be used in cases when the distance between the CF_3 group and the alkylating centre is shorter than three carbon atoms (Walborsky et al., 1955; Tsushima et al., 1988).

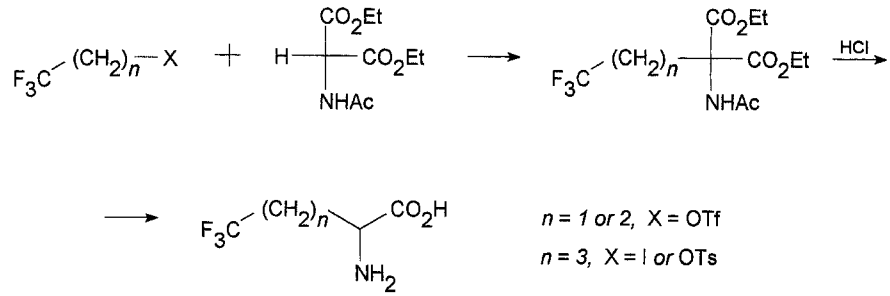

Fig. 16

The alkylation of acetamidomalonic ester may be brought about also by Michael addition, as documented by the syntheses of 4-fluoroglutamic acid (Hudlický, 1960, 1961) and 4,4,4-trifluorovaline (Taguchi et al., 1985).

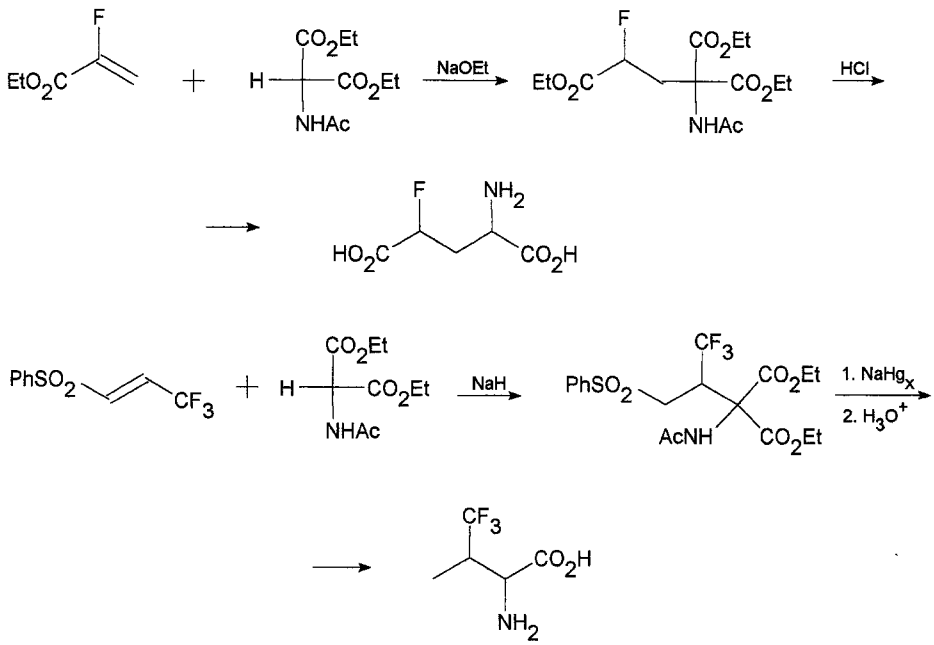

Fig. 17

Within the last two decades a new modification of the acetamidomalonic ester synthesis has been developed, based on the alkylation of the Schiff bases derived from aminomalonic (Tsushima and Kawada, 1985) and various 2-aminomonocarboxylic esters (Bey and Vevert, 1978; Bey et al., 1979, 1984; Tsushima et al., 1985) As alkylating agents, diverse fluorohalomethanes were frequently applied. Many fluorinated 2-amino acids were synthesized by this modern variation on the classical theme in a simple manner.

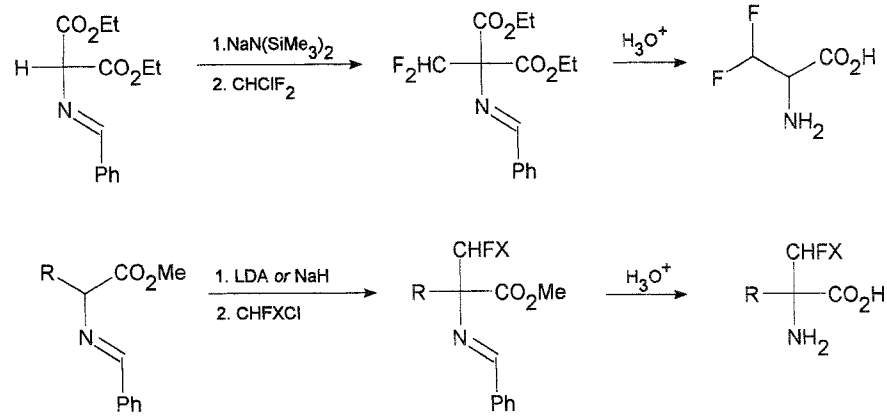

Fig. 18

Instead of Schiff bases, substituted acetoacetic esters were also used in a similar sequence of reactions. After alkylation, the t-butyl ester is converted into the acyl azide, which then undergoes the Curtius rearrangement to the carbamate (Bey et al., 1984; Bey and Schirlin, 1978; Schirlin et al., 1992).

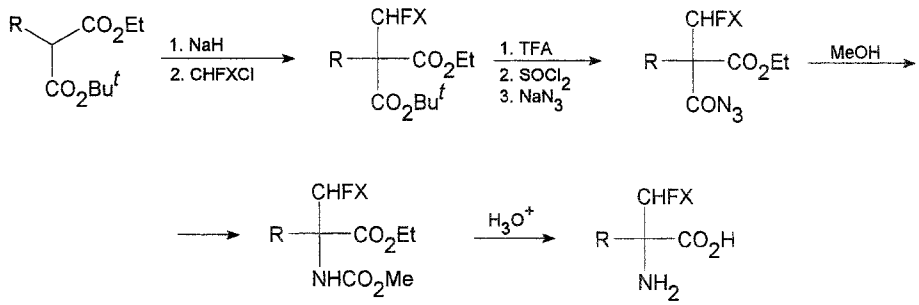

Fig. 19

Both the Schiff base and the acetoacetic ester routes were successfully employed in the synthesis of the very promissing antimalarial 2-difluoromethylornithine in good overall yields (Bey and Schirlin, 1978; Bey et al., 1979).

Modern synthetic routes

During the intense development of fluorine chemistry, which began within and after the Second World War and lasts until the present time, many new

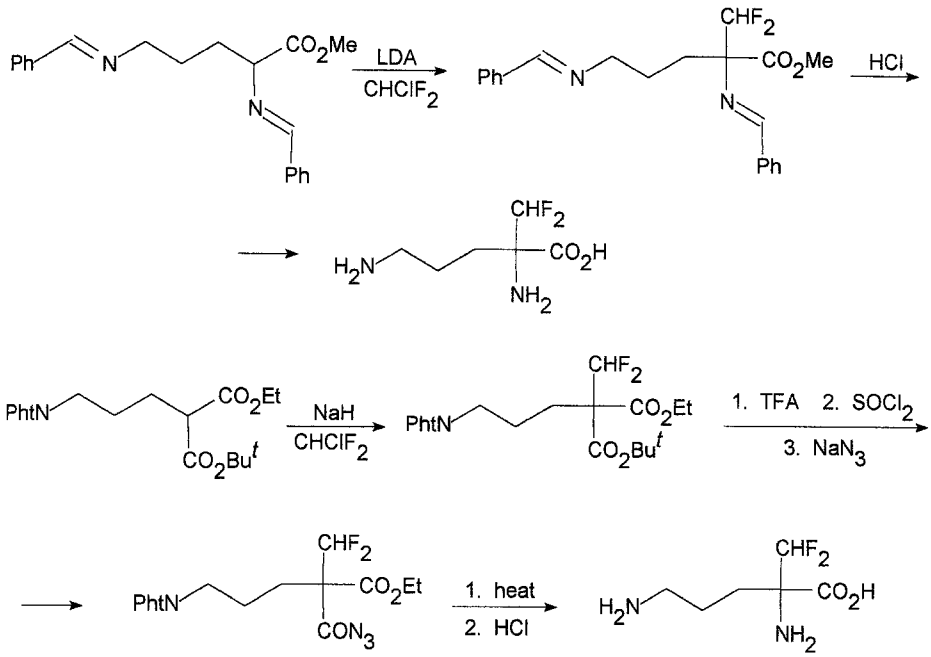

Fig. 20

fluoroorganic compounds were synthesized, useful as synthons in the preparation of fluoro amino acids. Also, new fluorinating agents, which enable us to introduce fluorine or fluorine-containing groups into the molecule either within the synthetic pathway or into the non-fluorinated amino acid as such, have been discovered and made available. Their exploitation gave rise to numerous fluorinated analogues of diverse amino acids, many of them being unattainable by the classical chemistry.

Among the modern syntheses of fluoro amino acids, perhaps the most attractive are those based on introduction of fluorine or fluorine-containing group directly into the parent amino acid. In some cases, protection of the functional groups is unnecessary. Although these electrophilic fluorinations often suffer from the lack of regioselectivity, they process, on the other hand, with complete retention of stereochemistry.

(S)-Phenylalanine, on treatment with diluted fluorine yields a mixture of all three isomeric (S)-fluorophenylalanines (Coenen et al., 1986). Whereas unprotected tyrosine is converted by the element exclusively to the 3′-fluoro derivative, the N,O-diacetyl-L-tyrosine methyl ester yields a mixture of the both ring-monofluorinated isomers (Chirakal et al., 1987). Also the unprotected 3′,4′-dihydroxyphenylalanine (DOPA) is converted by fluorine into all three monofluoro derivatives (Firnan et al., 1984, 1986). Fluorination in the aliphatic part of molecule was observed in the reaction of fluorine with phenylpyruvic ester; the resulting β-fluorophenylpyruvate was further converted into *erythro*-β-fluorophenylalanine by reductive amination (Tsushima et al., 1984).

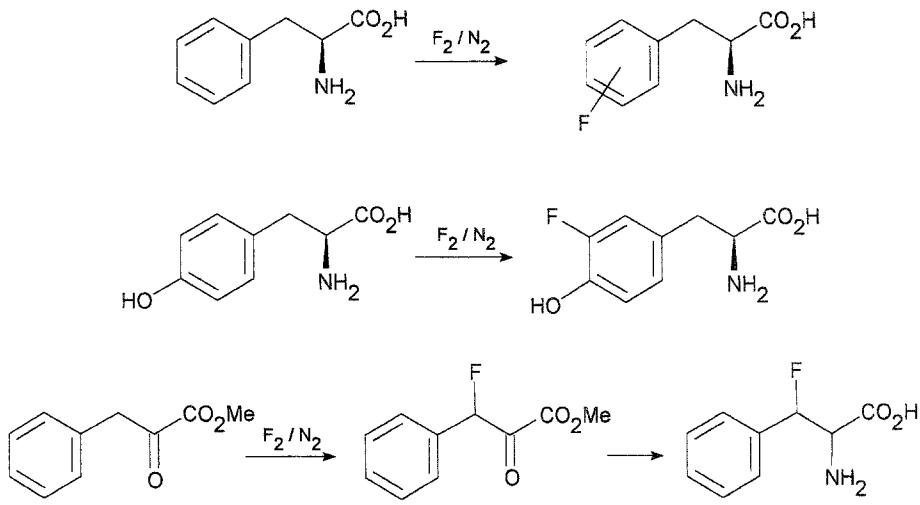

Fig. 21

Fluorodesulfuration of cysteine by fluorine leads to the mixture of 3-fluoroalanine and 3,3-difluoroalanine with the former as the major component (Kollonitsch et al., 1976).

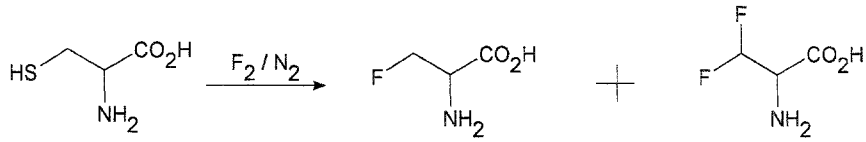

Fig. 22

Aromatic fluorinations have been realized also by the use of xenon difluoride and acetyl hypofluorite with results similar to those of direct fluorinations by the element (Black et al., 1988; Firnau et al., 1980). Unprotected DOPA gave a mixture of 2′- and 6′-fluoroDOPA on treatment with acetyl hypofluorite (Adam et al., 1986). To attain regiospecific substitution, fluorodemercuration of a mercurated precursor is the method of choice (Luxen et al., 1986; Luxen and Barrio, 1988).

For their mildness and short reaction times, these reagents are frequently used in the preparation of ^{18}F-labelled compounds for use in medicine. Also, as sensitive compounds as the peptides have been successfully fluorinated either by fluorine (Hebel et al., 1970) or by acetyl hypofluorite (Garrett et al., 1991).

Another reagent from the same group, namely trifluoromethyl hypofluorite has been applied for direct conversion of unprotected aliphatic amino acids into their fluoro derivatives. Under UV irradiation, action of the reagent on alanine gives rise to 3-fluoroalanine (Kollonitsch and Barash,

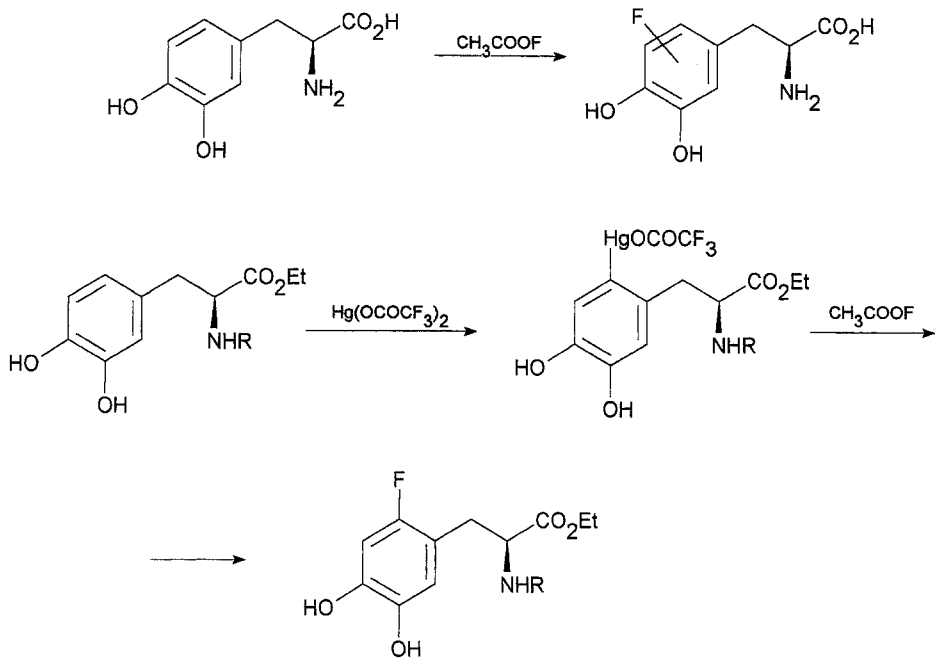

Fig. 23

1976); 3,3-difluoro and 3,3,3-trifluoroalanine were also prepared in this way (Kollonitsch, 1976). Analogously, aspartic acid yields 3-fluoroaspartic acid (Kollonitsch, 1976), 2-methylglutamic acid is fluorinated in the methyl group, giving 2-fluoromethylglutamic acid (Kollonitsch et al., 1970) and lysine is converted into 5-fluorolysine (Curtley and Hirschmann, 1983).

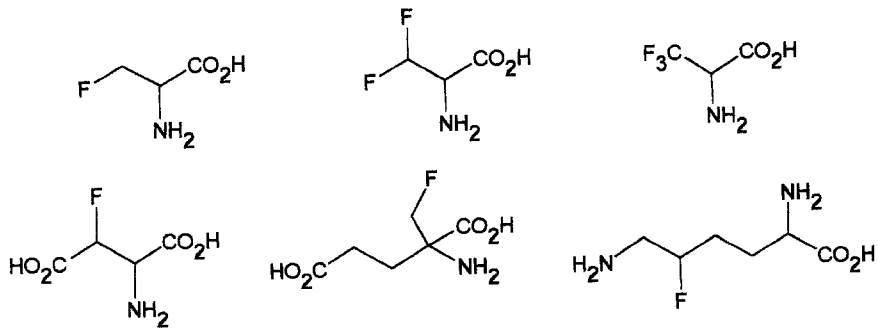

Fig. 24

The CH-acidic compunds may be converted into the CF-derivatives by treatment with perchloryl fluoride. It has been employed several times also in the synthesis of fluoro amino acids, as demonstrated on the synthesis of 4-fluoroglutamic acid (Tolman and Vereš, 1967) and 3,3-difluoroaspartic acid (Hageman et al., 1977). Unfortunately, the explosive character of perchloryl fluoride discriminates it from being a routine laboratory reagent (Fig. 25).

For the exchange of oxygen-containing functions for fluorine, several reagents are known which differ in their reactivity and applicability. As shown on Fig. 25, 4-fluoroglutamic acid was prepared by a safer way than above by the action of the Yarovenko reagent (2-chloro-1,1,2-trifluoroethyldiethylamine, YAR) on the appropriate 4-hydroxy ester with the glutamic acid skeleton (Bergmann and Chun-Tsu, 1973).

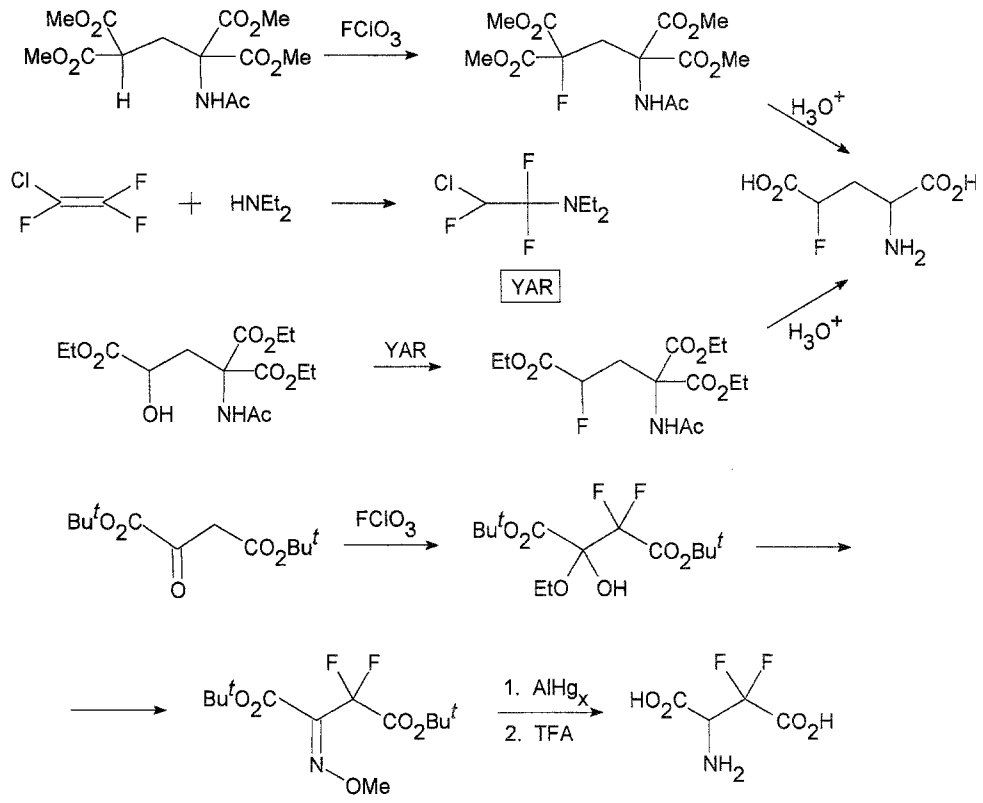

Fig. 25

The use of the Yarovenko reagent is restricted to the exchange of the hydroxy group for fluorine. More versatile than this compound is sulfur tetrafluoride and compounds derived therefrom, diethylaminosulfurtrifluoride (DAST) and its methyl analogue, methyl-DAST. A number of fluoro amino acids, including the sensitive β-fluoro amino acids, was prepared from the corresponding hydroxy amino acids on treatment with sulfur tetrafluoride (Kollonitsch et al., 1975, 1979; Shirota et al., 1977; Reider et al., 1987). Protected hydroxy- and oxo amino acid derivatives may be converted, under the action of sulfur tetrafluoride, into the mono- and difluoro amino acids, respectively, as documented by the synthesis of 4-fluorolysine (Curtley and Hirschmann, 1983) and 5,5-difluorolysine (Shirota et al., 1977).

The use of DAST for the same functional transformations is shown on the synthesis of 2-fluoro- and 2,2-difluoro analogues of the neurotransmitter 4-aminobutyric acid (GABA) from one hydroxy precursor (Hoshi et al., 1990).

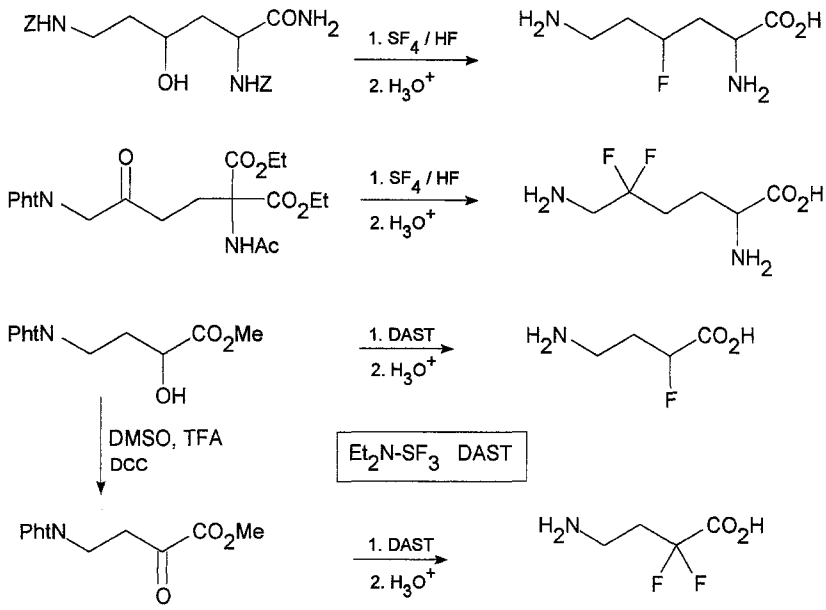

Fig. 26

The stereospecifity of fluorodehydroxylation by DAST, which proceeds with inversion of configuration is demonstrated on Fig. 27, showing the elegant synthesis of all four stereoisomers of 4-fluoroglutamic acid from the respective 4-hydroxyprolines. The absolute configuration of the 4-fluoroglutamic acid stereomers was thus determined (Hudlický and Merola, 1990; Hudlický, 1993).

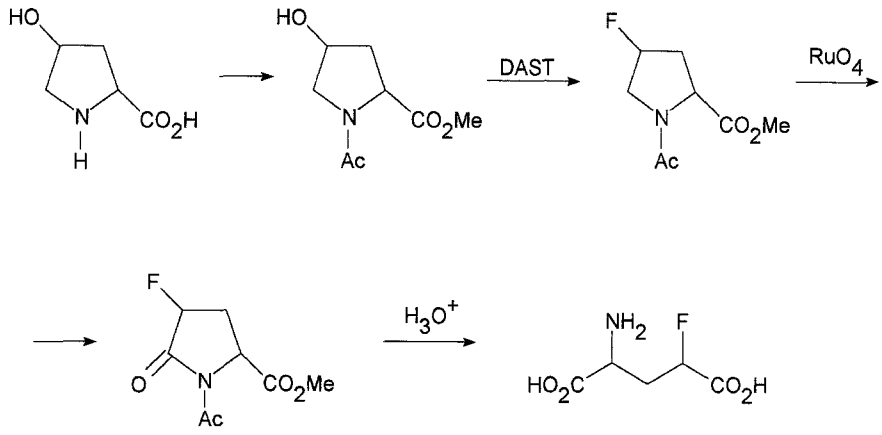

Fig. 27

In the synthesis of 2-trifluoromethyl derivatives of amino acids, esters of trifluoropyruvic acid and diverse imines derived therefrom are very valuable synthons. The general reaction between the N-protected imino esters and organometallic reagents makes a great number of 2-trifluoromethyl amino acids available in a simple manner. This reaction, shown on Fig. 28, as well as

other 2-trifluoromethyl amino acid syntheses, has recently been reviewed (Sewald and Burger, 1995).

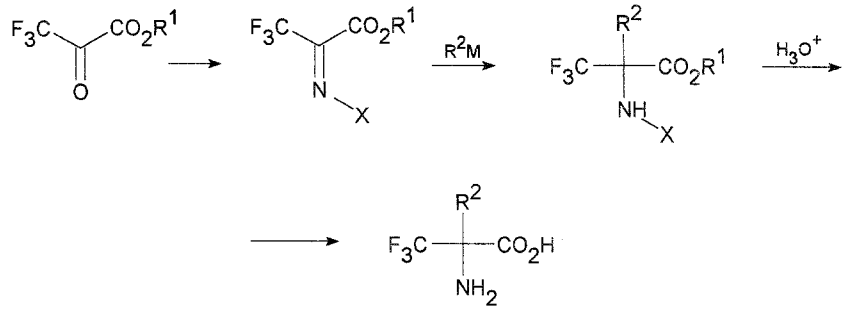

Fig. 28

A new way of introducing the amino function into the molecule of a fluorinated precursor, developed in the last decade, is based on the amidocarboxylation of fluorinated aldehydes or alkenes. 4,4,4-Trifluorovaline and 5,5,5-trifluoronorvaline were synthesized in high yields from the respective trifluorobutanals on treatment with acetamide under high pressure of carbon monoxide/hydrogen mixture at 120°C, dicobalt octacarbonyl being the catalyst. The N-acetylamino acids formed were either hydrolyzed by acid to give racemic trifluoro amino acids, or were resolved by *acylase I* into the antipodes of high sterical purity (Ojima et al., 1989). Similar amidocarboxylation of 3,3,3-trifluoropropene yielded a mixture of both fluorinated acetylamino acids in a ratio depending on the catalyst used. Catalysis by dicobalt octacarbonyl resulted in preferential formation of the norvaline derivative, while the use of mixed rhodium + cobalt carbonyls led to the branched-chain amino acid. The selectivity was about 95% in both cases (Ojima et al., 1985).

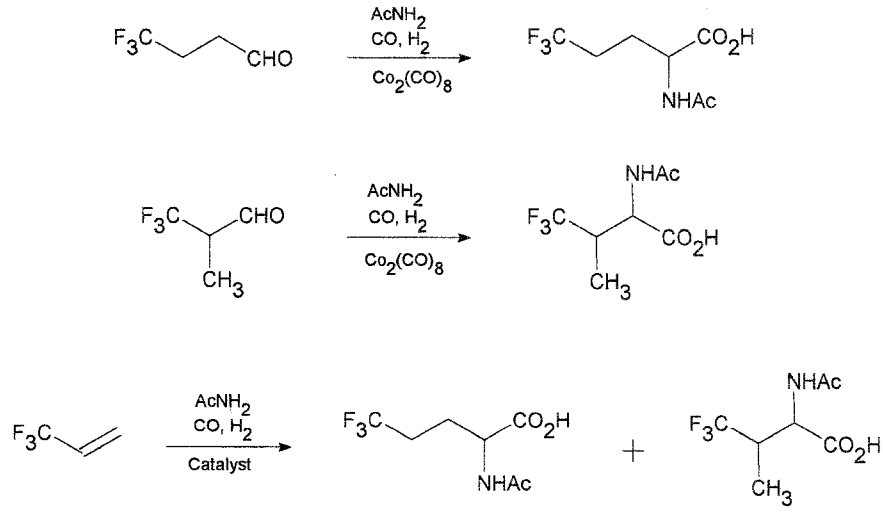

Fig. 29

Finally, let's mention the modern syntheses of three fluoro derivatives of a sulphur-containing amino acid methionine. Only the monofluoro amino acid, 6-fluoromethionine may be prepared from the protected parent amino acid by direct fluorination by xenon difluoride (Jansen et al., 1983). 6,6-Difluoromethionine resulted from the action of chlorodifluoromethane on either free homocysteine (Tsushima et al., 1990) or its N-acetyl derivative (Houston and Honek, 1989). 6,6,6-Trifluoromethionine is formed in a photochemical trifluoromethylation of homocysteine (Soloshonok et al., 1992) or N-acetylhomocysteine (Houston and Honek, 1989) by iodotrifluoromethane.

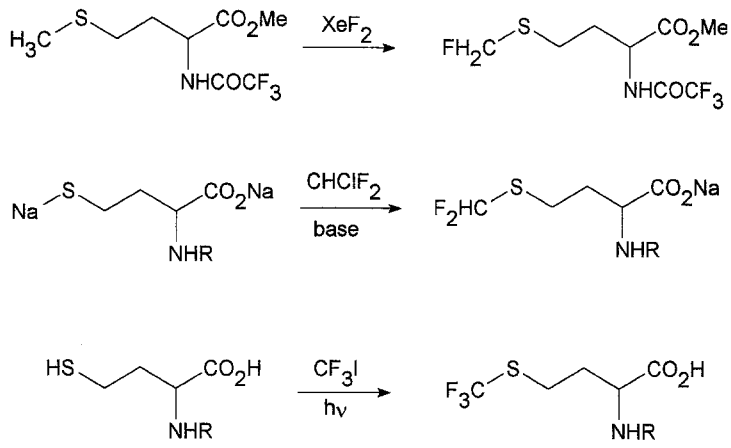

Fig. 30

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