FLUORINE--CONTAINING AMINO ACIDS SYNTHESIS & PROPERTIES

Fluorine-containing Amino Acids

Synthesis and Properties

Edited by
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Preface

The interest in amino acids (AAs) and their derivatives has existed for many years. More than 700 AAs have already been found in nature and their number is continually growing. Investigations into the biological properties of these AAs have been intensively prosecuted and have resulted in a dramatic acceleration of activity and interest in synthesis of unusual AAs directed, first of all, at the creation of new medicines and fine biochemicals. The synthesis of unusual AAs has continued to develop at a tremendous pace over the past 40 years, producing an incredible range of structurally exotic and novel compounds. The man-made area of fluorine-containing amino acids (FAAs) takes the most important place in the family of unusual AAs.

The upsurge in interest in FAA chemistry and biology has a number of origins. Among these, the similar geometry of FAAs to hydrocarbon patterns, the opposite polarization of C—H and C—F bonds and greater energy of the latter, have played a major part. Biologists and medicinal chemists have been quick to seize on the opportunities opened up by these unique basic physicochemical properties of FAAs. It is an exciting story to see how chemists and biologists have inspired each other to build up the field of FAAs. It is a field to which both chemists and biologists have contributed significantly. The present brisk activity in the field, with the surprises that often emerge from research in this area, recently led Professor D. Seebach to coin a new term, *Flustrates* (*Flu*orine-containing sub*strates*). Being on the borderline between the organic chemistry and life science fields, FAAs possess enormous potential for future development. Suffice to say that the biochemistry of FAAs is still in its infancy. The origin of the biological activity of a number of FAAs has been studied, but these studies have not involved systematic investigations, but rather relatively random sampling. The application of FAAs in peptide design is also in the early stages of development.

The motives of authors of scientific books are as many and varied as the authors themselves. In our case we decided to edit this book mostly because we are in love with the subject. Also, we believe that the time is now ripe for a book in which the chemistry of FAAs and the existing knowledge of their biological properties are brought together and examined critically. We have attempted to produce a book as complete and comprehensive as the current state of knowledge and practical space limitations will permit. It was the enthusiastic consensus of the publisher, editors and contributors to achieve

this goal. The individual authors have been given a great deal of freedom in preparing their contributions so that personal viewpoints could be presented and new, unpublished results could be disseminated.

Chapters 1–3 deal with a synthesis of FAAs by methods of classical amino acid chemistry, organofluorine chemistry and organometallic chemistry. Chapter 4 devoted to the synthesis of fluoroamino acids containing fluorine atom(s) in the β-position to the amino group. Among this type of FAAs the specific inhibitors of polyamine biosynthesis have been discovered. In the area of FAAs, which are mostly optically active, it is not possible to be successful without the preparation and investigation of individual stereoisomers (enantiomers) of these compounds. We have devoted four chapters to this aspect. Chemical and enzymatic asymmetric syntheses of FAAs are described in Chapters 5 and 6 and the enzymatic and chromatographic resolution of racemic FAAs in Chapters 7 and 8. In the final chapters, the biological properties of FAAs and their applications are reviewed. We hope that the contributions by ourselves and fifteen distinguished scientists collected in this volume will stimulate new ideas and initiate further research in all areas of FAAs chemistry and biology.

The chemistry of FAAs is only one part of a large field of biologically active organofluorine compounds. One can see growing interest in the chemistry and biology of fluorine-containing nucleosides, vitamins, steroids and carbohydrates and also new pharmaceuticals, pesticides and other biologically active substances. Obviously, we are still at the very beginning of crucial changes in scientific and industrial activities directed to the investigation, production and application of fine organofluorine compounds. The future of the field is assured by the results obtained so far and many new avenues of research await further interdisciplinary investigation.

The readership for which we have geared this book is research workers in the field of organic chemistry and organofluorine chemistry in general, medicinal and pharmaceutical chemists and others who are interested in the synthesis of organoelement analogues of natural compounds. The volume is designed as a source book and general reference and not as a textbook. It contains much that is of practical use to working chemists and biochemists in the identified fields.

We are grateful to all of the contributing authors for their dedication to the subject. Without their efforts this book could not have seen the light of day. We also thank Miss Jenny Cossham, Elspeth Tyler, Martin Röthlisberger and Irene Cooper (of John Wiley & Sons) for their pleasant cooperation and their toleration of several last-minute changes. Finally, the editors mutually acknowledge their unflagging support during the various stages of the enterprise.

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1993

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1 Syntheses of Fluorine-containing Amino Acids by Methods of Classical Amino Acid Chemistry

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1.1 INTRODUCTION

The term 'methods of classical chemistry' should be understood only as a writer's licence, not as an explicit definition of any particular area created by exactly specified synthetic reactions. Of course, there is no doubt about the 'classical' character of most of the reactions reviewed in this chapter. Nevertheless, some cases *do* exist in which, for example, the synthesis is modified by 'modern' access to a 'classical' intermediate, or when a 'classical' starting compound is transformed into the product in a 'modern' way, but the *strategy* of the synthesis remains unchanged. The question necessarily arises of where the borders are. The answer may be a matter of discussion, but in this chapter the author will conform to the needs of practice. As a logical consequence, occasional overlapping with other chapters is inevitable.

Among the very numerous syntheses of fluorine-containing analogues of amino acids, those using the methods of classical amino acid chemistry are, on the whole, conceivably among the first pathways which the synthetic chemist takes into consideration and evaluates for their utility for the preparation of a desired fluorinated compound. This access is based on two premises: (1) stability and chemical inertness of the C—F bond(s); and (2) similar reactivities of the fluorinated and non-fluorinated reactants.

Provided that both of these hypotheses are valid, the concept of preparing fluoroamino acids by following the syntheses of their non-fluorinated counterparts represented a viable synthetic strategy and, as such, it was very frequently and successfully applied. However, this point of view is only a one-sided and mechanistic one, as it does not take into account the extreme electronegativity of fluorine (the standard electrode potential of F is 2.65 V, referred to the H^+/H couple as zero). This fact, in its consequences, is responsible for the limited applicability of the methods described in this chapter. The limitation is caused by:

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(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 polyfluorinated compounds;
(3) the formerly unexpected considerable lability of the C—F bonds in a β- and, to some extent, also in a γ-position to carbonyl.

Despite these limitations, many fluorinated amino acids have been successfully prepared by classical methods. The syntheses will be described in the following sections:

1.2 Amination and related reactions.
1.3 The Strecker synthesis.
1.4 The hydantoin synthesis.
1.5 The Erlenmeyer azlactone synthesis.
1.6 Syntheses using *N*-substituted aminomalonic esters and related compounds.
1.7 Syntheses involving other CH-acidic esters. The Curtius and Schmidt rearrangements.
1.8 Syntheses from 2-oxo acids and their derivatives.
1.9 Fluorinated amino acids from other amino acids.
1.10 Miscellaneous syntheses.

1.2 AMINATION AND RELATED REACTIONS

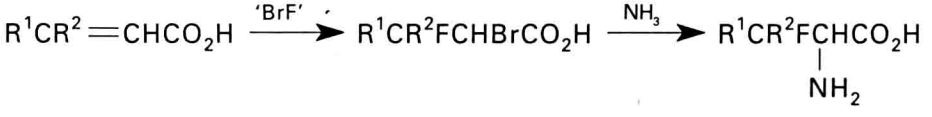
In this section, attention will be given to all reactions in which the amino group is introduced by direct reaction of ammonia or its equivalents with halo and hydroxy compounds (either free or as the sulfonate esters) and with compounds possessing carbon–carbon double bonds or an oxirane ring. As the ammonia equivalents we shall consider, for the purpose of this section, phthalimide and its potassium salt, azide ion and, in particular cases, also hexamethyldisilazane, dibenzylamine and trifluoroacetamide.

The simplest fluorinated amino acid, 3-fluoro-2-alanine (**1**) and its nearest homologue, 2-amino-4-fluorobutyric acid (**2**), were prepared in a two-step synthesis by bromination and ammonolysis of the appropriate alkanoic acids [1].

$$F(CH_2)_nCH_2CO_2H \xrightarrow{Br_2} F(CH_2)_nCHCO_2H \xrightarrow{NH_3(l)} F(CH_2)_nCHCO_2H$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad Br \qquad\qquad\qquad\qquad\qquad\qquad\quad NH_2$$

(**1**) $n = 1$
(**2**) $n = 2$

A series of homologous 2-amino-3-fluorocarboxylic acids were prepared similarly starting from the corresponding alk-2-enoic acids, which were first bromofluorinated with a mixture of *N*-bromoacetamide and hydrogen fluoride and then ammonolysed [2].

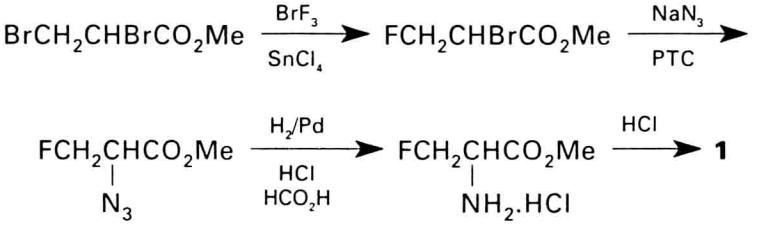


(1), (3)–(6)

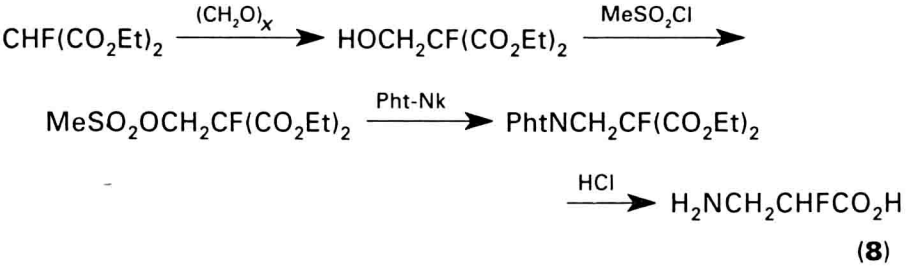
(**1**) $R^1 = R^2 = H$ 3-fluoro-2-alanine
(**3**) $R^1 = Me$, $R^2 = H$ 2-amino-3-fluorobutyric acid
(**4**) $R^1 = Et$, $R^2 = H$ 3-fluoronorvaline
(**5**) $R^1 = Pr$, $R^2 = H$ 3-fluoronorleucine
(**6**) $R^1 = Bu$, $R^2 = H$ 2-amino-3-fluoroheptanoic acid

One branched-chain amino acid, 3-fluorovaline (**7**) ($R^1 = R^2 = Me$) has been also synthesized by this approach.

In addition to direct amination, the amino acid **1** has also been prepared recently from methyl 2-bromo-3-fluoropropionate by converting it under phase-transfer catalysis into the appropriate 2-azido ester, which was then hydrogenated under carefully controlled conditions to the methyl ester of **1**. In order to avoid the simultaneous loss of fluorine during the reduction step, the hydrogenation was carried out in methanol–formic acid solution with saturation with hydrogen chloride [3].

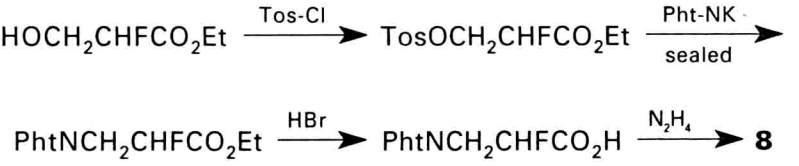


The isomer of **1**, 2-fluoro-3-alanine (**8**), resulted as the final product of two syntheses, both using potassium phthalimide as the aminating agent. Starting from diethyl fluoromalonate, amino acid **8** was prepared in four steps [4].

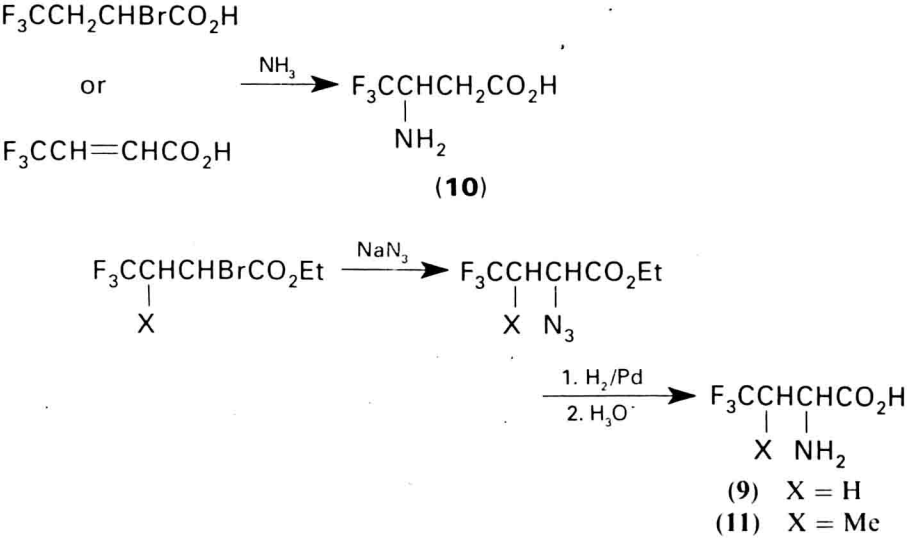


(8)

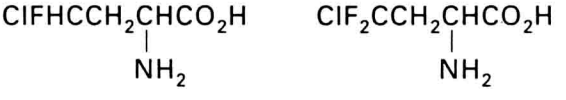
While this synthesis is a 'pure' substitution of the esterified hydroxy group, the other access to **8**, starting from ethyl 2-fluoro-3-hydroxypropionate, involves an elimination–addition mechanism [5].



In the attempted preparation of 2-amino-4,4,4-trifluorobutyric acid (**9**) by reaction of either 2-bromo-4,4,4-trifluorobutyric acid or 4,4,4-trifluorocrotonic acid with ammonia, the isomeric 3-amino-4,4,4-trifluorobutyric acid (**10**) was the sole product. The strong electronegativity of the trifluoromethyl group was responsible for this unintentional result; however, this problem was successfully circumvented by reacting the bromo ester with sodium azide and hydrogenolysis of the 2-azido ester [6].

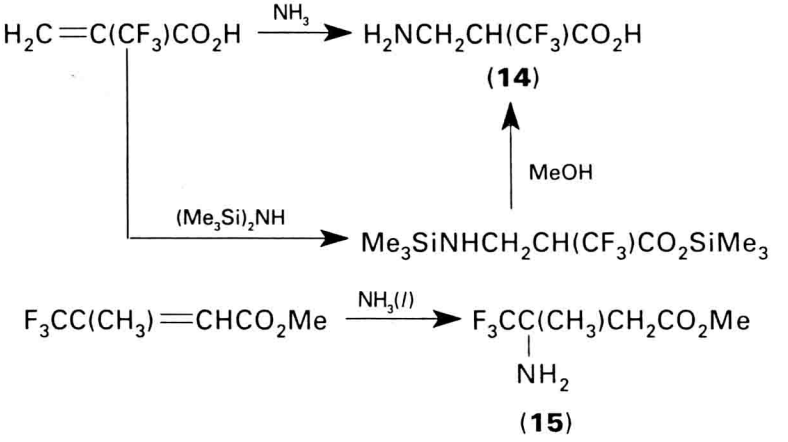


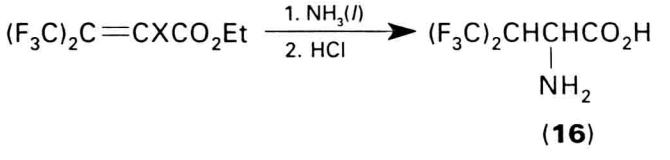
In the same way, 4,4,4-trifluorovaline (**11**) was also prepared [7]. This methodology has been successfully applied also for the synthesis of 2-amino-4-chloro-4-fluorobutyric acid (**12**) and of 2-amino-4-chloro-4,4-difluorobutyric acid (**13**), the corresponding 2-chloro esters being the starting compounds [8].



(12) **(13)**

2-(Trifluoromethyl)acrylic acid has been found to add ammonia or hexamethyldisilazane fairly easily to give quantitatively [9] the 3-amino acid 3-amino-3′,3′,3′-trifluoroisobutyric acid (**14**); analogously, from methyl 3-methyl-4,4,4-trifluorocrotonate the methyl ester of 3-amino-3-methyl-4,4,4-trifluorobutyric acid (**15**) was prepared [10]. On the other hand, replacement of the 3-methyl group in the unsaturated ester by the second trifluoromethyl leads to the reversal of polarity of the double bond, so that the 2-amino acid 4,4,4,4′,4′,4′-hexafluorovaline (**16**) is the final product [11, 12, 13].

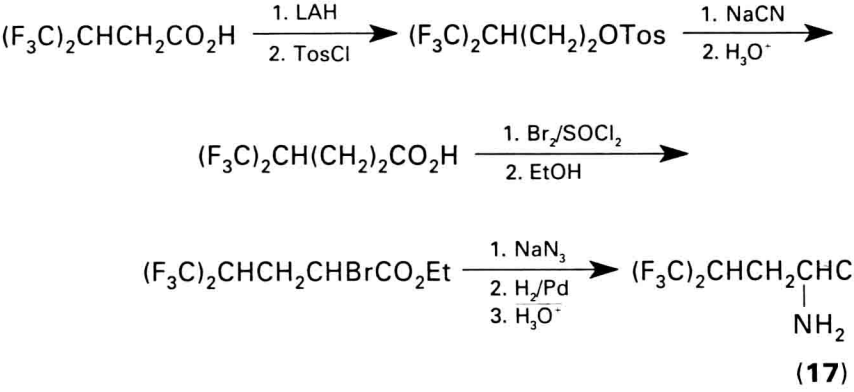




(16)

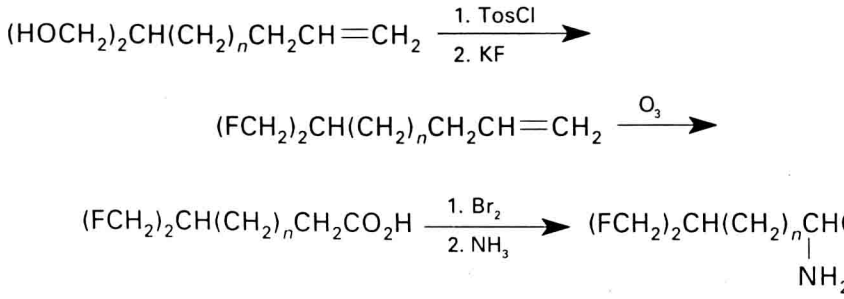
X = H [11,12]
X = CO_2Et [13]

The homologous 5,5,5,5′,5′,5′-hexafluoroleucine (**17**) resulted from a multistep synthesis, involving the chain elongation of the starting 3-(trifluoromethyl)-4,4,4-trifluorobutyric acid [14].



(17)

Ammonolysis of the 2-bromo acid was also the final step in the synthesis of two difluorinated amino acids. 4,4′-difluorovaline (**18**) and 5,5′-difluoroleucine (**19**). The toluenesulfonates of the starting 2-(alk-2′- or -3′-en-1′-yl)-propane-1,3-diols were converted into the unsaturated 1,3-difluorides, which on ozonolysis and subsequent bromination yielded the pertinent 2-bromo acids [1].



(18) $n = 0$
(19) $n = 1$

An elegant access to amino acids containing a terminal perfluoroalkyl group was based on the free radical addition of perfluoroalkyl iodides to ethyl acrylate; the resulting fluorinated 2-iodo esters were converted into the amino acids using the azide route [15]:

$$R_f I + H_2C{=}CHCO_2Et \longrightarrow R_fCH_2CHICO_2Et$$

$$\xrightarrow[\substack{2.\ H_2/Pd\\ 3.\ H_3O^+}]{1.\ NaN_3} R_fCH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCO_2H$$

	(9)	(20)	(21)	(22)
R_f =	CF_3	C_2F_5	C_3F_7	$(CF_3)_2CF$

Similar addition [16] of perfluoropropyl iodide to but-3-enoic acid and diethyl allylmalonate, respectively, followed by reductive removal of iodine from the primary adducts led to the heptafluoro derivatives of heptanoic and octanoic acids, which were then brominated and finally aminated to give 2-amino-5,5,6,6,7,7,7-heptafluoroheptanoic acid (**23**) and 2-amino-6,6,7,7,8,8,8-heptafluorooctanoic acid (**24**).

$$H_2C{=}CHCH_2CO_2H \xrightarrow[AIBN]{C_3F_7I} F_3C(CF_2)_2CH_2CHICH_2CO_2H \xrightarrow[2.\ Br_2]{1.\ Zn}$$

$$F_3C(CF_2)_2(CH_2)_2CHBrCO_2H \xrightarrow{NH_3} F_3C(CF_2)_2(CH_2)_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCO_2H$$

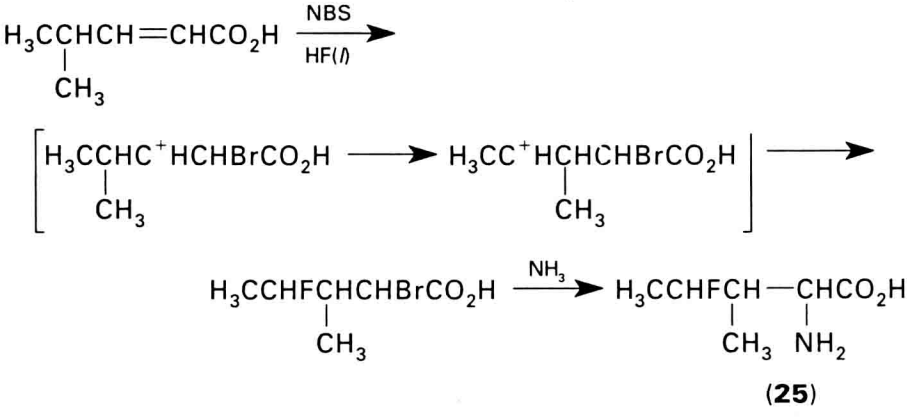
(23)

$$H_2C{=}CHCH_2CH(CO_2Et)_2 \xrightarrow[AIBN]{C_3F_7I} F_3C(CF_2)_2CH_2CHICH_2CH(CO_2Et)_2$$

$$\xrightarrow[2.\ KOH]{1.\ Zn} F_3C(CF_2)_2(CH_2)_3CH_2CO_2H \xrightarrow[2.\ NH_3]{1.\ Br_2} F_3C(CF_2)_2(CH_2)_3\underset{\displaystyle NH_2}{\underset{|}{C}}HCO_2H$$

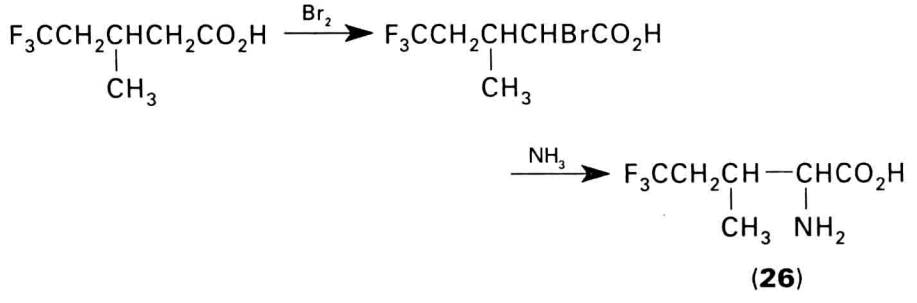
(24)

In the isoleucine series, Gershon *et al.* [17] used the anomalous result of bromofluorination of 4-methylpent-2-enoic acid in the synthesis of 4-fluoroisoleucine (**25**). The originally formed 3-carbocation rearranged by the methyl group transfer to the thermodynamically more stable 4-carbocation, which then added fluoride anion to give 2-bromo-4-fluoro-3-methylpentanoic acid; this on treatment with ammonia yielded **25**.



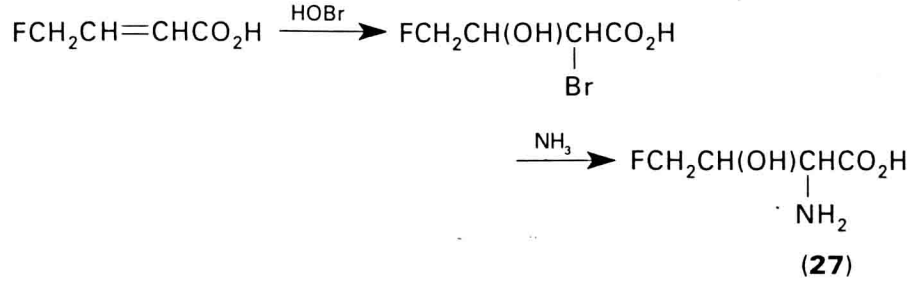
(25)

In another study, the methyl ester of the same bromo acid was converted into **25** via the azide method; however, the yield was very poor [18]. On the other hand, a good result has been reported in the synthesis of 5,5,5,-trifluoroisoleucine (**26**) from the parent 3-methyl-5,5,5-trifluoropentanoic acid [19]:



(26)

4-Fluorothreonine (**27**) (probably the *allo* form) was prepared from 4-fluorocrotonic acid by adding the elements of hypobromous acid, following by ammonolysis of the 2-bromo-4-fluoro-3-hydroxybutyric acid so formed [1]. 4,4,4-Trifluorothreonine (**28**), also as the *allo* isomer, resulted from the stereoselective opening of the *trans*-oxirane carboxylic ester by ammonia [20].



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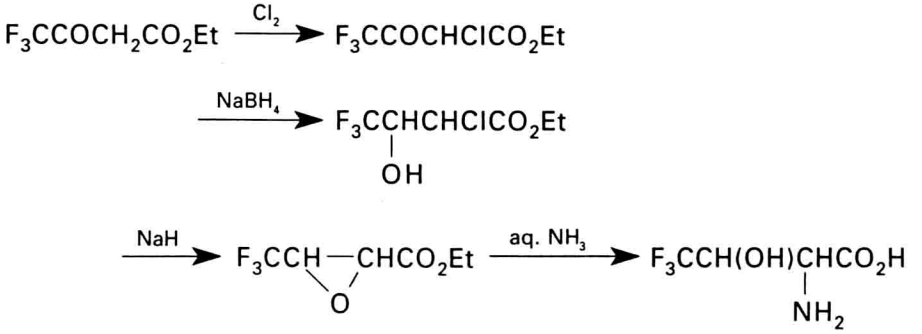
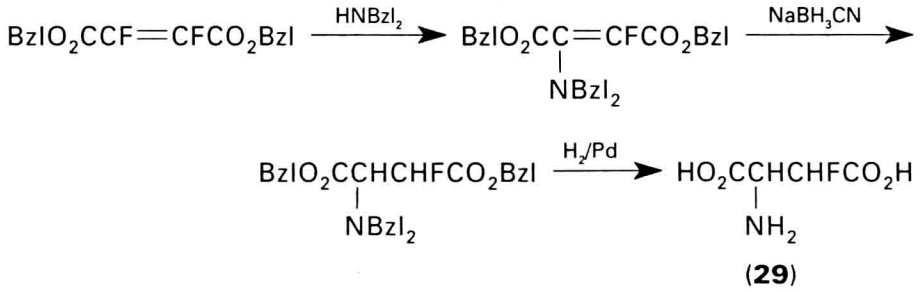


(28)

The simplest member of the monoaminodicarboxylic acid group, 3-fluoroaspartic acid (**29**), was the product of a three-step synthesis, starting with dibenzyl 2,3-difluoromaleate [21]. The high reactivity of fluorine in this ester permitted the successful introduction of one dibenzylamino group with the formation of an enamine ester, which was in turn reduced with sodium cyanoborohydride to dibenzyl 2-(*N*,*N*-dibenzylamino)-3-fluorosuccinate. Removal of all protecting groups by hydrogenolysis yielded **29**.



(29)

4,4-Difluoroglutamic acid (**30**) has recently been synthesised from methyl difluoroiodoacetate [22]. This ester is first converted into difluoroketene methyl triethylsilyl acetal, which adds on 3-acryloyl-4-phenyloxazolid-2-one to give the 5′-methyl ester of 3-(4′,4′-difluoro-1′-glutaryl)-4-phenyloxazolid-2-one. By sequential treatment of this compound with dibutylboron triflate, *N*-bromosuccinimide and sodium azide, the 2′-azido derivative was prepared, which after hydrogenolysis and deprotection gave **30**.