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Syntheses of γ-fluoro-α-amino acids

Review Article

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Summary. Methods for the synthesis of racemic and optically active title compounds are presented. Key step of these four-step procedures is the alkylation with 1-bromo-2-fluoroalkanes of glycine-ester-derived imines in anhydrous medium using lithium diisopropylamide as a base at low temperature or phase transfer catalyzed alkylation with 50% NaOH and triethylbenzylammoniumchloride as the phase transfer catalyst, respectively. Subsequent three-step deprotection gave the free acids in 13–33% overall yield. Deracemization of γ-fluoro-α-aminobutyric acid methyl and ethyl esters with α-chymotrypsin was shown to give the (−)-enantiomers of the esters and (+)-γ-fluoro-α-aminobutyric acid in >98% ee, while from the *tert*-butylester the opposite stereochemical result was observed giving the (−)-acid with 88% ee. Optically active γ-fluoro-α-amino acids were synthesized alternatively by phase transfer catalysis with N-benzyl-cinchonium chloride or using an auxiliary-directed asymmetric alkylation of the imine derived from (R)-(+)-camphor or (R)-(+)-2-hydroxypinan-3-one. These processes gave different enantiomers of γ-fluoro-α-aminobutyric acid via a monomeric lithium enolate in the first or a dimeric lithium enolate in the second case, respectively. The enantiomeric excess can be improved by lithium/magnesium exchange.

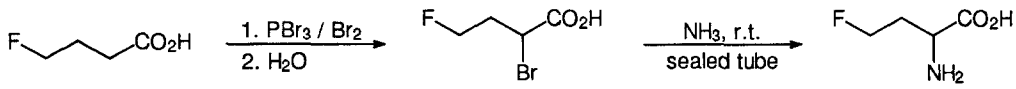
Keywords: Amino acids – Fluorinated amino acids – Alkylation – Glycine esters – 1-Bromo-2-fluoroalkanes

Fluorinated amino acids and derived peptides claim an extraordinary interest in chemistry and biochemistry as well as in medicinal research because of their enormous variety of biological activity. Moreover, the determination of conformations of these compounds becomes more effective using ^{19}F NMR spectroscopy.

γ-Fluoro-α-amino acids have been rarely synthesized in the past using only a limited number of methods. Nucleophilic substitutions of hydroxyl- or halo-

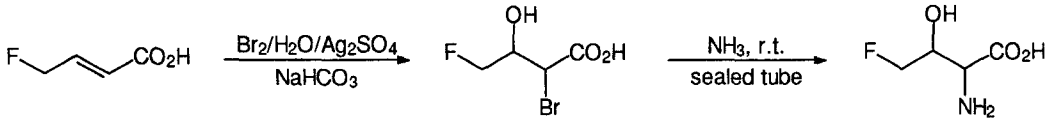
gen substituents with fluorine in the corresponding amino acids or of halogens with an amino group in fluorinated halocarboxylic acids have mostly been employed (Kukhar and Soloshonok, 1995).

Via this strategy Lettré and Wölcke (1967) synthesized γ-fluoro-α-aminobutyric acid (57% overall yield) by bromination of γ-fluorobutyric acid and subsequent reaction of the α-bromo compound with liquid ammonia.



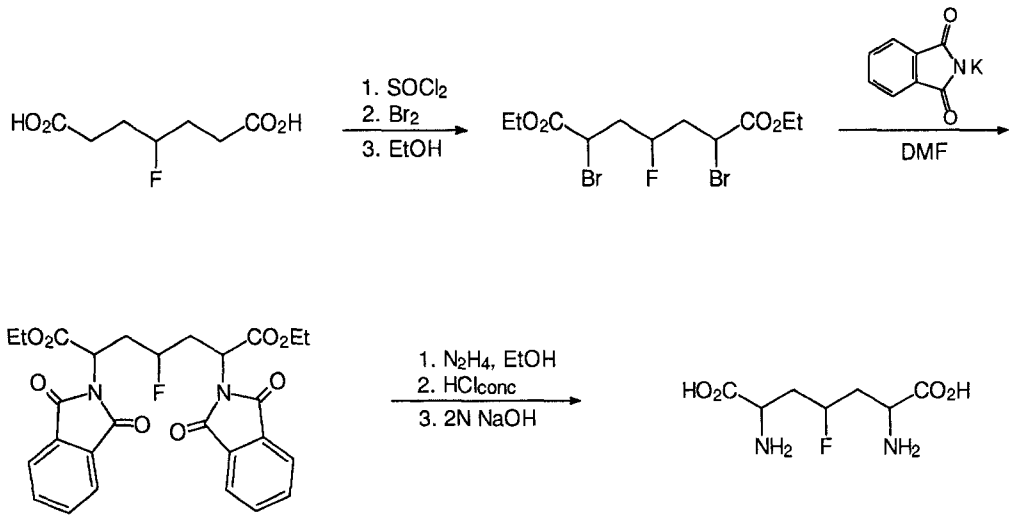
Scheme 1

Similarly γ-fluoro-threonine has been prepared, probably as a mixture of diastereomers, from γ-fluorocrotic acid by bromohydroxylation and subsequent nucleophilic substitution of bromine by ammonia, however with only 4% overall yield (Lettré and Wölcke, 1967).



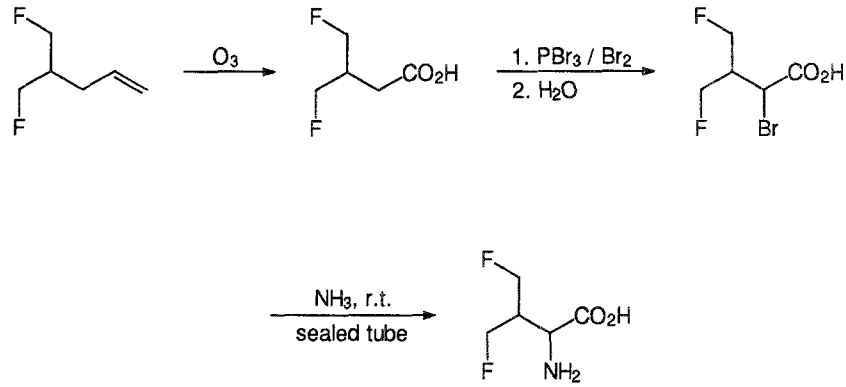
Scheme 2

α,α'-Diamino-γ-fluoropimelic acid has been prepared in a three-step procedure starting from γ-fluoropimelic acid in 17% overall yield (Cavalleri et al., 1966). In a one-pot reaction first diethyl α,α'-dibromo-γ-fluoropimelate (81%) and subsequently the bis-phthalimide (71%) was synthesized which on hydrazinolysis and subsequent acid hydrolysis gave the fluorinated amino acid (30%).



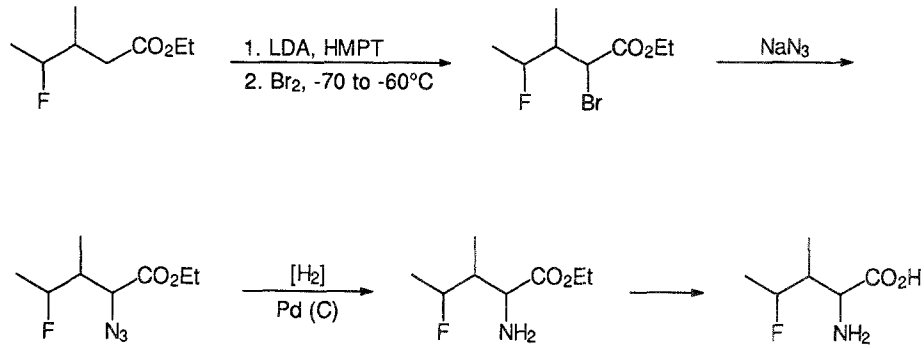
Scheme 3

A similar procedure has been employed for the synthesis of D,L-γ,γ′-difluorovaline. Starting from 2-allyl-1,3-difluoropropane on ozonolysis γ,γ′-difluoroisovaleric acid was obtained. Bromination and subsequent nucleophilic substitution gave the fluorinated amino acid with 11% overall yield (Lettré and Wölcke, 1967).



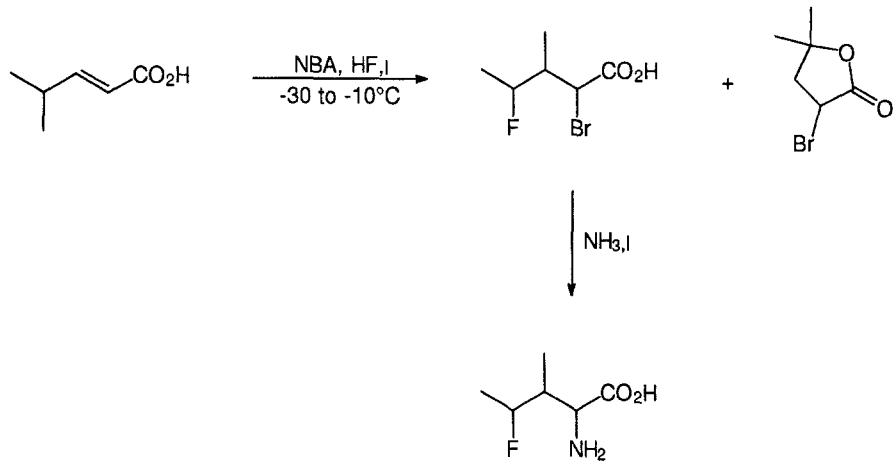
Scheme 4

Similarly, γ-fluoroisoleucine has been synthesized from 4-fluoro-3-methyl-pentanoate which was first brominated in 2-position. Subsequent nucleophilic substitution with azide and reduction to the amino group gave the amino acid ester. After hydrolysis the fluorinated acid has been isolated in very low yield (Butina and Hudlicky, 1980).



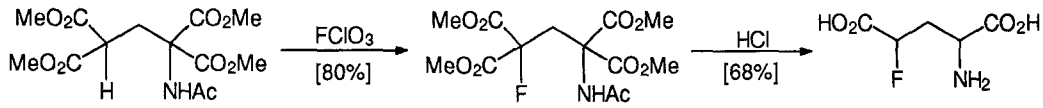
Scheme 5

The leaving group together with the fluorine atom can be introduced simultaneously into an unsaturated carboxylic acid by bromofluorination. By this route 4-fluoroisoleucine has been prepared in 4.7% overall yield from 4-methyl-2-pentenoic acid. On treatment with N-bromoacetamide in liquid hydrogen fluoride the acid gave 10.9% of 2-bromo-4-methyl-pentanoic acid and 60% of 2-bromo-4,4-dimethyl-4-butyrolactone. After separation the bromo substituent was replaced on treatment with liquid ammonia in a sealed stainless steel pressure vessel at room temperature (Gershorn et al., 1978).



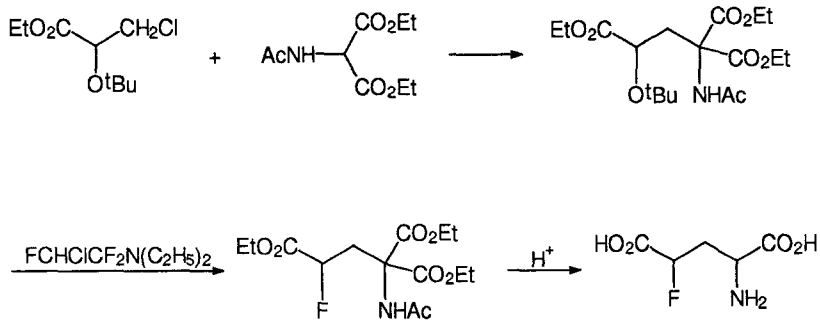
Scheme 6

γ-Fluoroglutamic acid has been prepared by direct fluorination with perchloryl fluoride of tetramethyl 2-acetamido-2,4-dicarboxyglutarate and subsequent hydrolysis with decarboxylation of the 4-fluoro tetracarboxylate in 54% total yield (Tolman and Vereš, 1966, 1967) or 58–66% yield (Alekseeva et al., 1967). Starting from this acid several derivatives like γ-fluoroglutamine have been synthesized (Tolman and Vereš, 1967).



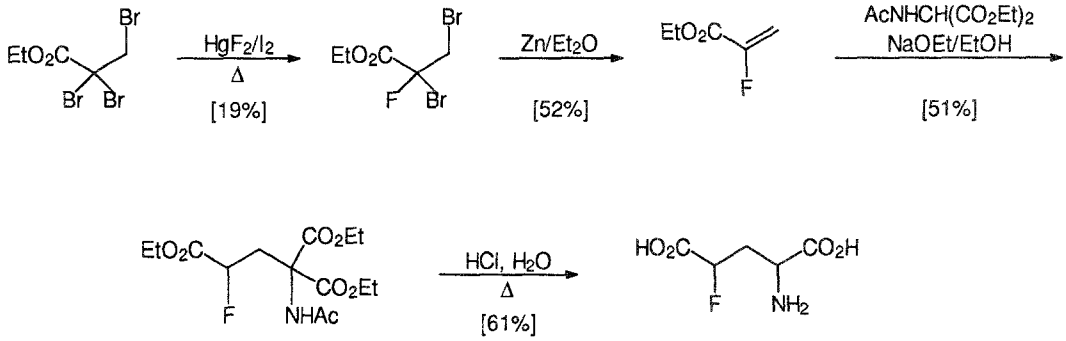
Scheme 7

One more method for the preparation of this acid has been developed by Bergmann and Chun-Hsu (1973). Treatment of ethyl 3-chloro-2-*tert*-butyloxypropionic acid with diethyl acetamidomalonate and subsequent substitution of the ether function by fluorine with Yarovenko's reagent (Yarovenko and Raksha, 1959) provides γ-fluoroglutamic acid.



Scheme 8

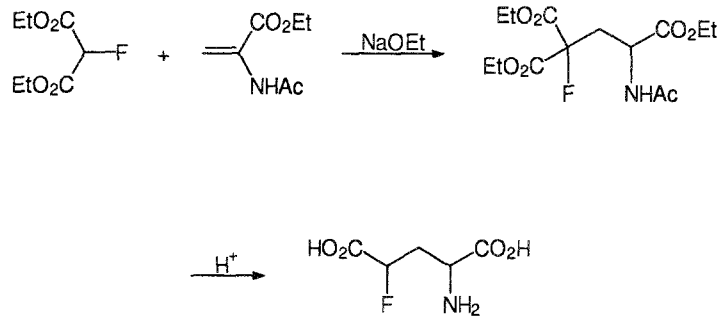
The construction of the carbon skeleton by formation of a carbon-carbon bond from a fluorinated and a non-fluorinated building block is another way to γ-fluoro-α-amino acids. Thus, Michael addition of acetamidomalonate towards ethyl α-fluoroacrylate (obtained from ethyl 1,1,2-tribromopropionate, 10% yield) gave γ-fluoroglutamic acid in 3.1% overall yield (Hudlický, 1960, 1961).



Scheme 9

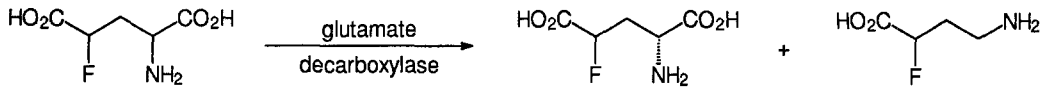
A significant improvement of the original procedure to prepare α-fluoroacrylate and the final fluorinated amino acid was described by Tolman et al. (1964, 1983, 1993).

Moreover, Hudlický's method (1960, 1961) can be used in a "reverse mode". Starting with diethyl 2-fluoromalonate as the C_3- and ethyl 2-acetamidoacrylate as the C_2-building block, the product is formed in 56% overall yield (Buchanan et al., 1962).



Scheme 10

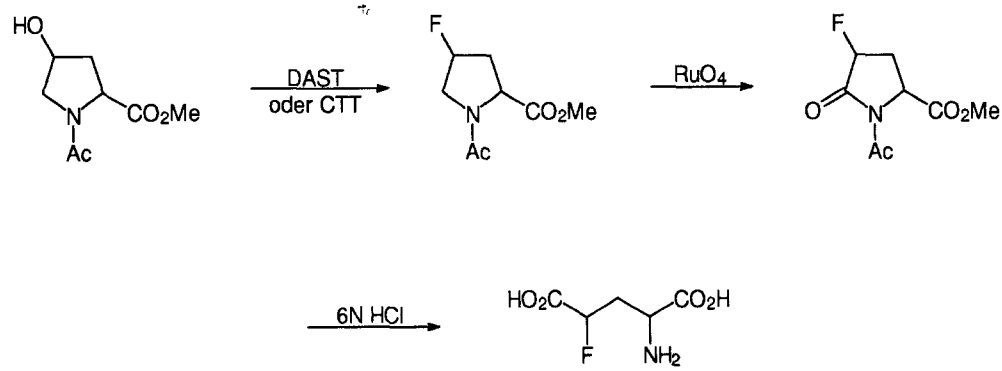
However, none of these methods to prepare γ-fluoroglutamic acid permits any stereoselectivity. For the separation of the two diastereomeric D-4-fluoroglutamic acids from the mixture of the four isomers Unkeless and Goldman (1970) used the enzyme glutamate decarboxylase. Therby, the L-diastereomers are decarboxylated to yield racemic α-fluoro-γ-aminobutyric acid while the diastereomeric D-4-fluoroglutamic acids can be recovered.



Scheme 11

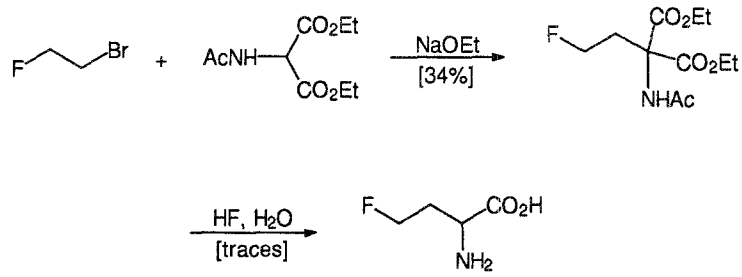
Unkeless and Goldman (1971) also reported the separation of the racemic erythro- and threo-diastereomers by ion-exchange chromatography and subsequent enzymatic separation of previous synthesized diastereomeric L-N-leucyl-D,L-4-fluoroglutamic acids by leucine aminopeptidase. Moreover, Bory et al. (1984) described the stereoselective hydrolysis of L-leucyl-γ-fluoro-D,L-glutamates by leucine aminopeptidase from porcine kidney with threo-γ-fluoroglutamate containing dipeptides in contrast to the lack of stereoselectivity in the case of the erythro-isomers.

All four stereoisomers of this acid have been synthesized from the respective stereoisomeric 4-hydroxyprolines by a three-step sequence. The N-protected cyclic amino acids gave the respective 4-fluoroprolines on fluorodehydroxylation by diethylaminosulfur trifluoride or Yarovenko's reagent with inversion of the configuration at C-4. Ruthenium tetraoxide oxidation converted the fluoroproline derivatives into protected lactames, which on hydrolysis gave the optically active 4-fluoroglutamic acids (Hudlický, 1993).



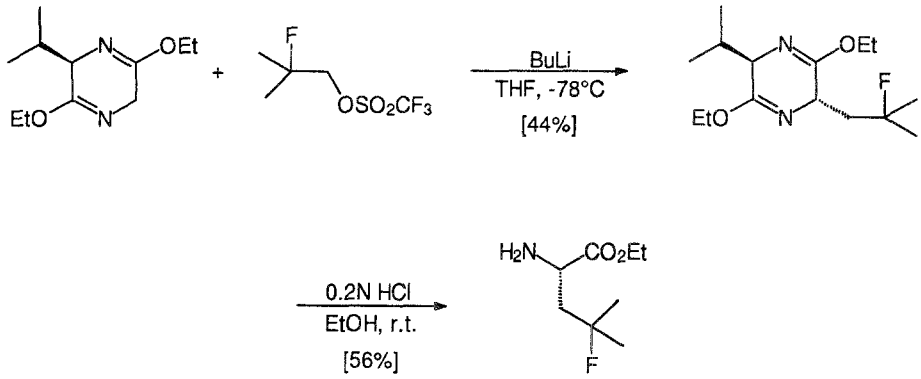
Scheme 12

ω-Fluoro-α-amino acids have also been synthesized from primary ω-fluoroalkyl bromides by condensation with diethyl acetamidomalonate. This method is very successful to obtain 5-fluoronorvaline and 6-fluoronorleucine, however, the yield of diethyl acetamido(2-fluoroethyl)malonate is only moderate (35%). On hydrolysis with aqueous HF 60–92% of the theoretical amount of fluorine was lost. The desired 4-fluoro-2-aminobutyric acid could not be isolated in pure form (Raasch, 1958).



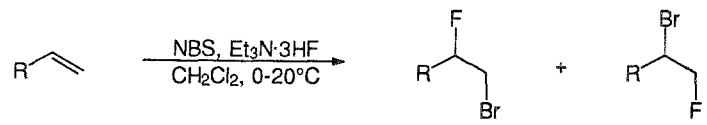
Scheme 13

Similar alkylation reactions towards an optically active γ-fluoro-α-amino acid has been used first by Papageorgion et al. (1994). Key step of the synthesis of (+)-γ-fluoroleucine ethyl ester is an alkylation following Schöllkopf's (1983) bis-lactimether methodology. (R)-2,5-Dihydro-3,6-diethoxy-5-isopropylpyrazine [cyclo-(D-Val-Gly)-bis-lactimether] is treated with butyl lithium and 2-fluoro-2-methyl-propyltriflate (available from isobutene in four steps) in tetrahydrofuran at −78°C. The alkylation product (44%) is partially hydrolyzed with 0.2N HCl in ethanol at room temperature to give the ethyl γ-fluoroleucinate (56%).



Scheme 14

The idea of our approach (Haufe and Kröger, 1995) was to use vicinal haloalkylfluorides as alkylating agents of glycine derivatives. 1-Bromo-2-fluoroalkanes are readily available by bromofluorination of terminal alkenes using a combination of N-bromosuccinimide and triethylamine trishydrofluoride (Haufe et al., 1987, 1996). This very useful reagent is not as dangerous as liquid HF or Olah's reagent (Py·9HF). Furthermore, it does not attack borosilicate glass and thus, can be handled in usual laboratory glassware.

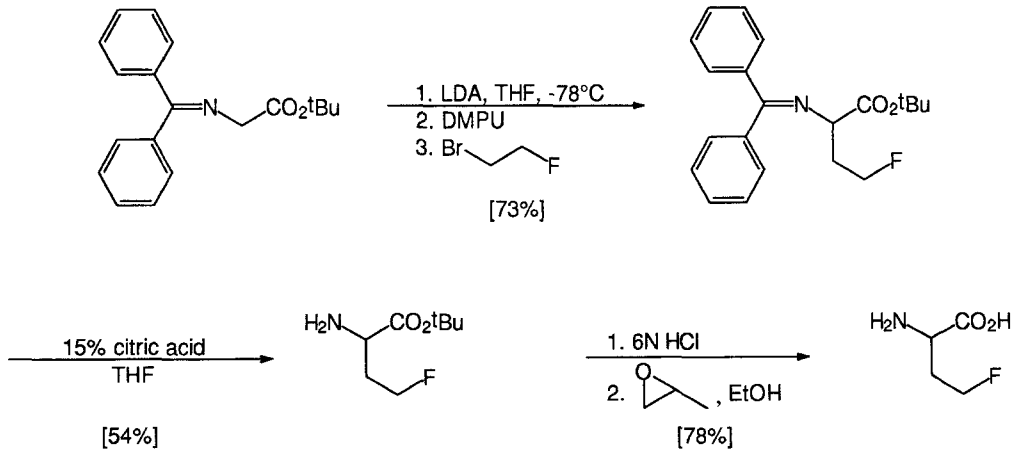


Scheme 15

The reaction is highly regioselective giving preferred the secondary fluoro compounds (ratio >9:1) in an overall yield of >90%. Moreover, it is not necessary to separate the regioisomers because the minor compounds do not react in the alkylation procedure.

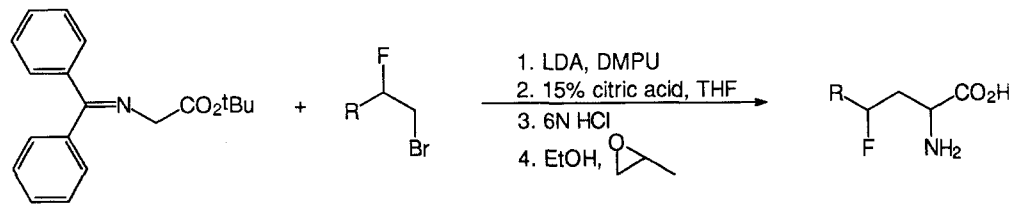
We started our investigation with alkylations of the Schiff's base derived from glycine *tert*-butylester and benzophenone. This type of alkylation is more difficult with vicinal bromofluorides compared with reactions of simple alkyl bromides or ω-fluoroalkyl bromides (Kröger, 1996). The fluorine substituent in β-position causes an increased electron density decreasing the electrophilicity of this alkylating agent.

However, the alkylation in analogy to the reaction with ethylbromide (O'Donnel et al., 1978) proceeds quite smoothly with bromofluoroethane giving the protected *tert*-butyl γ-fluoro-α-aminobutyrate in 73% yield. Hydrolysis of the imino function with 15% citric acid and subsequent ester hydrolysis with 6N hydrochloric acid gives the amino acid hydrochloride. The free γ-fluoro-α-aminobutyric acid has been obtained in 31% overall yield by treatment of the hydrochloride with propylene oxide in ethanol.



Scheme 16

Similarly other vicinal bromo fluoroalkanes and also 1-bromo-3-fluoropropane can be used for the alkylation process giving finally mixtures of the racemic diastereomers of γ-fluoronorvaline, γ-fluoronorleucine, some of their higher homologues, and δ-fluoronorvaline.



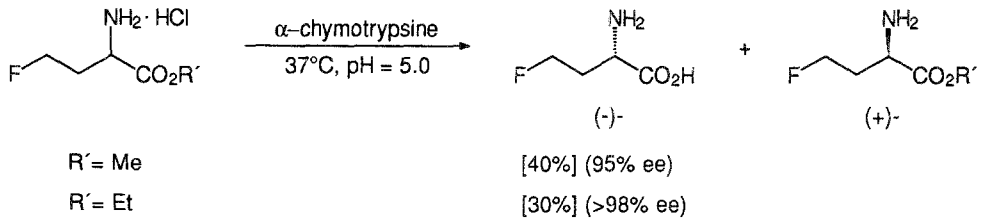
Scheme 17

Table 1. Synthesis of racemic γ-fluoro-α-amino acids

Entry	R	Overall yield (%)	Ratio of diastereomers (%)*
1	H	31	–
2	CH_3	28	42:58
3	C_2H_5	27	32:68
4	C_3H_7	22	34:66
5	$CH(CH_3)_2$	15	39:61
6	C_4H_9	14	20:80

*determined by ^{19}F-NMR spectroscopy.

The racemic mixture of different esters of γ-fluoro-α-aminobutyric acid (prepared as described for the *tert*-butylester) can be deracemized enzymatically using α-chymotrypsin.



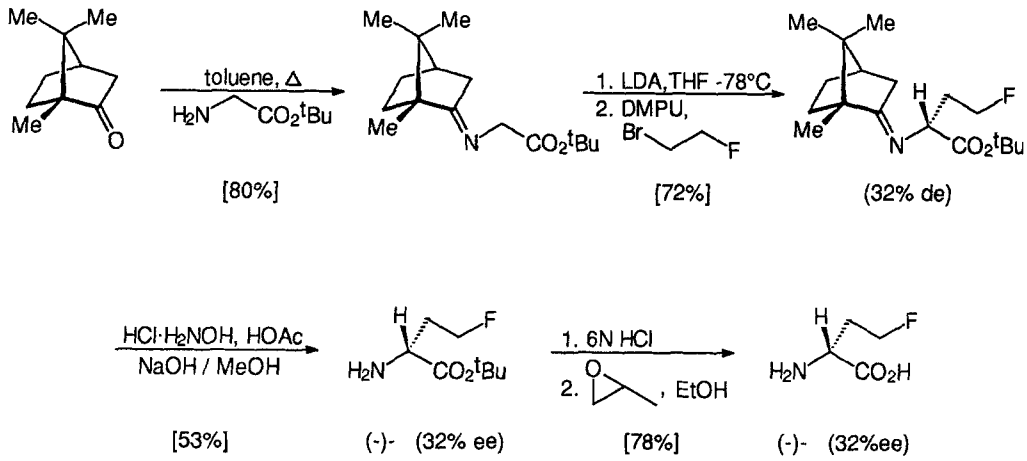
Scheme 18

The enzymatic cleavage of the methyl and the ethylesters gave the leavo rotatory amino acid and the dextrorotatory ester remained. Interestingly, the result of the hydrolysis of the *tert*-butylate using the same enzyme was found to be reverse. Best enantioselectivity (>98% ee) was obtained for the ethylester, while the methylester gave the best chemical yield (40%, 95% ee) of the (+)-2-amino-4-fluoro-butyric acid. Nearly the same enantioselectivity (88% ee) was found for the *tert*-butylester. However, in this case the (+)-enantiomer was hydrolysed, giving the (−)-2-amino-4-fluoro-butyric acid.

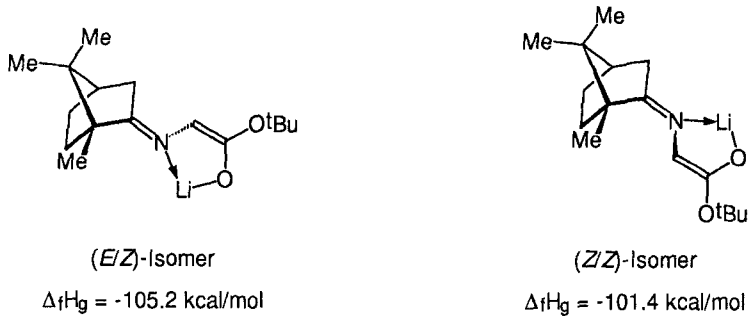
Based on results of Yamada et al. (1976), McIntosh et al. (1988) and Yaozhong et al. (1991) of diastereoselective syntheses of non-fluorinated amino acids we next examined an auxiliary directed alkylation employing bromofluoro ethane. The imine derived from (R)-(+)-camphor and glycine-*tert*-butylate on alkylation with bromofluoro ethane gave a 66:34 mixture of the diastereomers. This ratio can easily be determined by ^{19}F-NMR spectroscopy.

Deprotection in two steps gave the optically active γ-fluoro-α-aminobutyric acid in 30% overall yield based on (R)-(+)-camphor. The major product (32% ee) is the leavo rotatory enantiomer.

The mechanism of alkylation can be rationalized in terms of the formation of a cyclic lithium enolate. We calculated (PM3 method) the enthalpy of formation to be almost 4 kcal/mol lower for the (E,Z)-isomer in comparison to the (Z,Z)-isomer of the enolate in the gas phase.

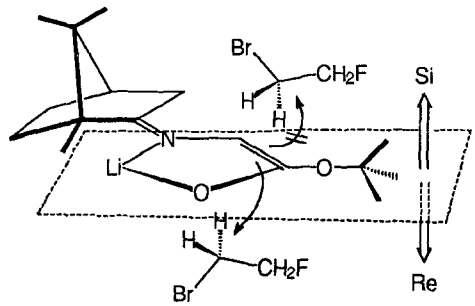


Scheme 19



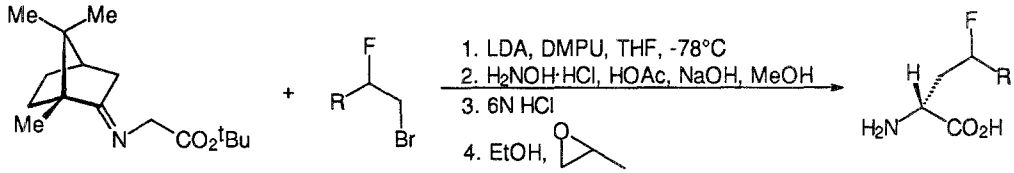
Scheme 20

The more stable enolate can be better alkylated from the Re-side (this is the endo-side in terms of the camphor skeleton) than from the Si-side.



Scheme 21

Using higher homologues of bromofluoroethane a kinetic deracemization is observed giving the two diasteromers. However, the diastereomeric excess is relatively low (24–50% de).



Scheme 22

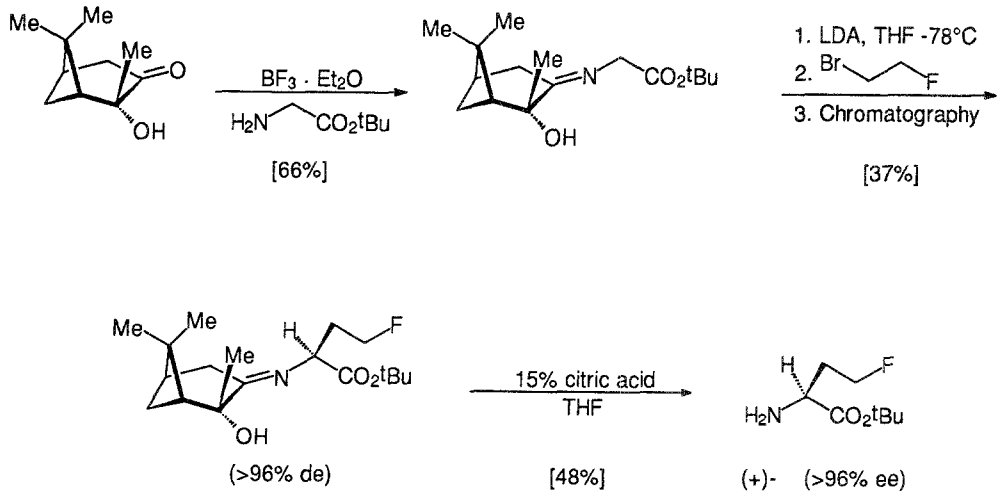
Table 2. Synthesis of optically active γ-fluoro-α-amino acids

Entry	R	Overall yield (%)	Ratio of diastereomers (%)*
1	H	25	–
2	CH_3	15	27:73
3	C_2H_5	10	25:75
4	C_3H_7	32	38:62
5	$CH(CH_3)_2$	32	37:63
6	C_4H_9	21	28:72

*determined by ^{19}F-NMR spectroscopy.

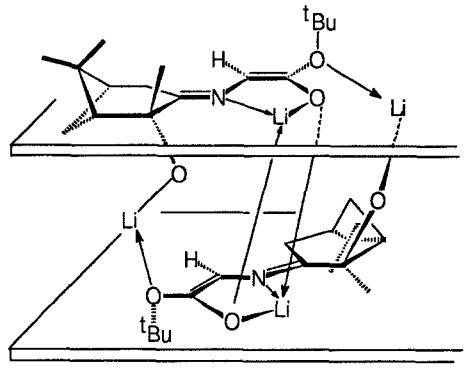
Variation of different parameters of this procedure such as temperature, solvent, addition of complexing agents like dimethylpropylen urea (DMPU) or tetramethyl ethylendiamine (TMEDA), or changing the relative amounts of the reactants did not significantly improve the selectivity.

Much better selectivity, however, was found in reactions with (R)-(+)-2-hydroxypinan-3-one, which was recommended for other alkylations by Yamada et al. (1976) and Oguri et al. (1978). Using this auxiliary derived from (S)-α-pinene the alkylation with bromofluoroethane gave a crude mixture (90:10) of two diastereomeric products. After chromatography only one diastereomer was isolated in 37% overall yield and >96% de.



Scheme 23

After hydrolysis it became obvious, that the dextro rotatory enantiomer of γ-fluoro-α-aminobutyric acid has been formed. However, inspection of models revealed that the same enantiomer like in the case of (R)-(+)-camphor should have been formed. This contradiction was solved in terms of the explanation given by Soladié-Cavallo et al. (1989, 1993) for other alkylations using the same auxiliary. The imine derived from glycine *tert*-butyrate and (R)-(+)-2-hydroxypinan-3-one forms an intermediary dimeric structure having C_2-symmetry. Obviously, alkylation can occur from both sides of the dimer leading to the same configuration at the alkylation position, but to the opposite one compared to the (R)-(+)-camphor derivative.



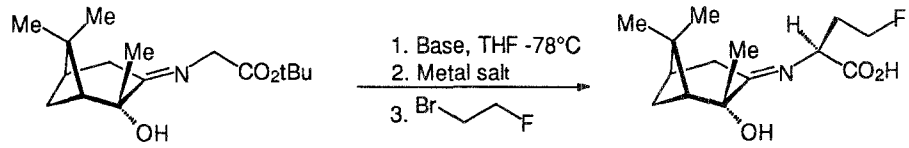
Scheme 24

The use of potassium *tert*-butylate as base leads to nearly complete loss of stereoselectivity, but gives good chemical yield. In contrast, the addition of 0.25 equivalents of $ZnCl_2$ (related to the base lithium diisoproylamide, LDA) gave the two diastereomers in 85:15 ratio, however, in very low yield. Addition of 0.25 equivalents of magnesium chloride lowered the selectivity while 0.5 equivalents improved the ratio of diastereomers to 2:98. In case of 1 equivalent a second diastereoisomer could not be detected any more. On the other hand, the chemical yield droped to 52% (GC).

Table 3. Alkylation of (R)-2-hydroxypinan-3-one based glycineester imide with 1-bromo-2-fluoroethane

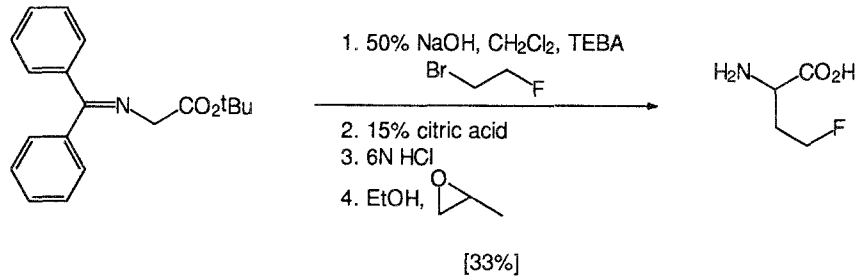
Entry	Metal ion	Base (2eq)	Metal salt (eq)	Yield (%) (GC)	Ratio of diastereomers (%)*
1	Li^+	LDA	–	74	12:88
2	K^+	KO^{t}Bu	–	77	58:42
3	Zn^{2+}	LDA	$ZnCl_2$ (0,5)	16	15:85
4	Mg^{2+}	LDA	$MgCl_2$ (0,5)	69	23:77
5	Mg^{2+}	LDA	$MgCl_2$ (1)	64	<2:98
6	Mg^{2+}	LDA	$MgCl_2$ (2)	52	<2:98

* determined by ^{19}F-NMR spectroscopy.



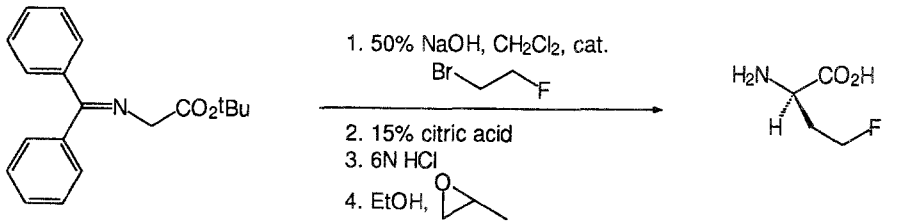
Scheme 25

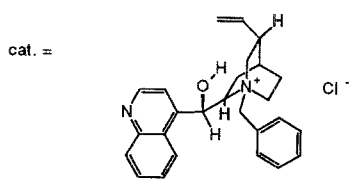
However, these four-step reactions are relatively expensive and the overall yields are only moderate. Thus, we tried alkylations in a two-phase system avoiding alkylations of lithium enolates under anhydrous conditions. Treatment of the imine derived from benzophenone and glycine *tert*-butyrate with bromofluoroethane and 50% aqueous sodium hydroxide in a two-phase system with methylene chloride in the presence of triethylbenzylammonium chloride (TEBA) gave the *tert*-butylester of γ-fluoro-α-aminobutyric acid in 33% overall yield after deprotection.



Scheme 26

N-Benzyl-(R)-cinchonium chloride was used as a chiral phase transfer catalyst to make this type of alkylation a stereoselective reaction. This catalyst has been recommended for this type of alkylations by O'Donnell et al. (1989). By this way the leavo rotatory γ-fluoro-α-aminobutyric acid has been synthesized in 24% overall yield with 38% enantiomeric excess.





(R)-N-Benzyl-cinchonium chloride

Scheme 27

Table 4. Comparison of pK values of some natural amino acids and its fluorinated analogues

Amino acid	pK_{COOH}	pK_{NH2}	ΔpK_{COOH}	ΔpK_{NH2}	pH_I
Alanine	2.4	9.9	–	–	6.1
β-Fluoroalanine	2.4	9.8	0	0.1	6.1
α-Aminobutyric acid	2.3	9.7	–	–	6
α-Amino-γ-fluorbutyric acid	2.4	9.2	−0.1	0.5	5.8
Trifluoromethylalanine	1.6	8.2	0.7	1.5	4.9
2-Amino-4-fluoro-5-methylhexanic acid	2.4	9.6	–	–	6.0
Norvaline	2.3	9.8	–	–	6.1
δ-Fluoronorvaline	2.3	8.8	0	1	5.6

ΔpK pK (unfluorinated amino acid) – pK (fluorinated amino acid).

As expected there is no significant influence of single fluorine substituent in β-, γ- or δ-position on the acidity of the respective carboxylic group. The γ-fluoro-α-aminobutyric acid is even slightly less acidic than the parent compound, while trifluoromethyl alanine is much more acidic. On the other hand there is an important decrease in the basicity of the amino group by 0.5 or 1.0 in terms of pKs values for γ-fluoro-α-aminobutyric acid compared to its parent compound or δ-fluoronorvaline in comparison to norvaline.

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