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β,γ-Alkynyl α-amino acids: a synthetic challenge

Review Article

P. Meffre and **F. Le Goffic**

Laboratoire de Bioorganique et Biotechnologies, associé au CNRS
École Nationale Supérieure de Chimie de Paris, Paris, France

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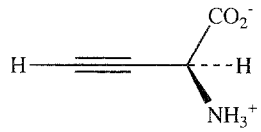
Summary. Ethynyl glycine is a naturally occurring unusual α-amino acid. Its known chemical and biological properties are summarized in the first part of this review. The second part is an overview on racemic syntheses of ethynyl glycine and other β,γ-alkynyl α-amino acid derivatives, including patent data. These small polyfunctional compounds revealed as being very labile and the synthesis of mainly fully or partially protected forms seemed to have been actually performed. The last part deals with the approaches to the enantioselective synthesis of β,γ-alkynyl α-amino acids derivatives, and details the only satisfactory strategy that has led to optically active β,γ-alkynyl α-amino acids derivatives up to now.

Keywords: Amino acids – Unusual amino acid – Ethynyl glycine – Alkynyl amino acids – Enzyme inhibitor – Antibacterial agent

1 Isolation, chemical and biological properties, structure elucidation of the naturally occurring Ethynyl glycine (Kuroda et al., 1980a,b)



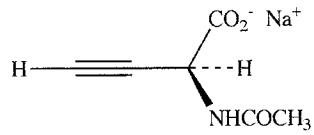
1

Ethynyl glycine **1** (FR-900130) was discovered in the course of a screening program of soil microorganisms producing substances exhibiting synergy with D-cycloserine. The secondary metabolite **1**, isolated from a fungus *Streptomyces catenulae*, is very labile in alkaline solution and decomposes very easily. It has been isolated in a very low yield as a light yellow

hygroscopic 70% pure powder. It shows antimicrobial activity against Gram-positive bacteria (no effect on Gram-negative bacteria) and acts synergistically with D-cycloserine: the activity against *Staphylococcus aureus* 279 is increased 16-fold by addition of 5μg/ml D-cycloserine. FR-900130 **1** causes spheroplast formation in an hypertonic medium suggesting that it appears to be a cell-wall biosynthesis inhibitor. Even though its inhibitory effect is not reversed by D-alanine, it can be expected to interfere with L-alanine racemase, a PLP dependent enzyme.

Some chemical properties of **1** have been examined. This compound seems to be stable at pH below 7.0: the activity is not affected at pH between 2 and 7 at 4°C for 60min. (aq. solution) and the residual activity is only 70% at pH 8.0 under the same conditions. However, no activity is detected after storage at 20°C for 12 hours. Moreover, concentrating and drying procedures cause loss of its activity. All these observations suggest that the primary amino function of FR-900130 participates to its stability by forming the hydrochloride salt.

FR-900130 was chemically characterized as its N-acetyl derivative **2** whose IR, ^{1}H and ^{13}C NMR spectra were recorded and interpreted as well as its elemental analysis determined.



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The acetyl derivative **2** of FR-900130 is a white powder, soluble in water, methanol and acetone and seems to be more stable than the original antibiotic **1**. The acidic form of compound **2** can be extracted from an aqueous solution (pH 1.4) with *n*-butanol but not with diethyl ether. Its behaviour in TLC has also been examined, it shows a negative reaction to the ninhydrine test. The optical rotation index is $[\alpha]_D^{20}$ + 37.5 (c 0.5, H_2O). It shows no activity *in vitro* against various bacteria tested but *in vivo* it is deacetylated into **1** which recovers its antibiotic activity. Finally, catalytic hydrogenation of the alkyne function (comparison with an authentic sample) and methylation with diazomethane, resp. (cyclisation products with participation of the triple bond) confirmed that FR-900130 **1** is L-2-amino-3-butynoic acid.

β,γ-unsaturated α-amino acids in general have received much attention in recent literature because it is now recognized that introducing an unsaturation in a strategic position of some enzyme substrates (allylamines, propargylamines, vinyl glycines, ...) introduces a substructure that renders that compound a conformationally constrained substrate analogue with potential mechanism-based inactivating properties (Abdulganeeva and Erzhanov, 1991; Abeles and Maycock, 1976; Abeles, 1980, 1983; Angst, 1987; Bey, 1989; John, 1980; Jung et al., 1979; Jung, 1985; Maycock et al., 1979; Metcalf and Sjoerdsma, 1979; Nagata and Yamaguchi, 1979; Rando, 1974abc, 1975, 1976, 1978, 1979, 1984; Stark and Bartlett, 1983; Walsh, 1982).

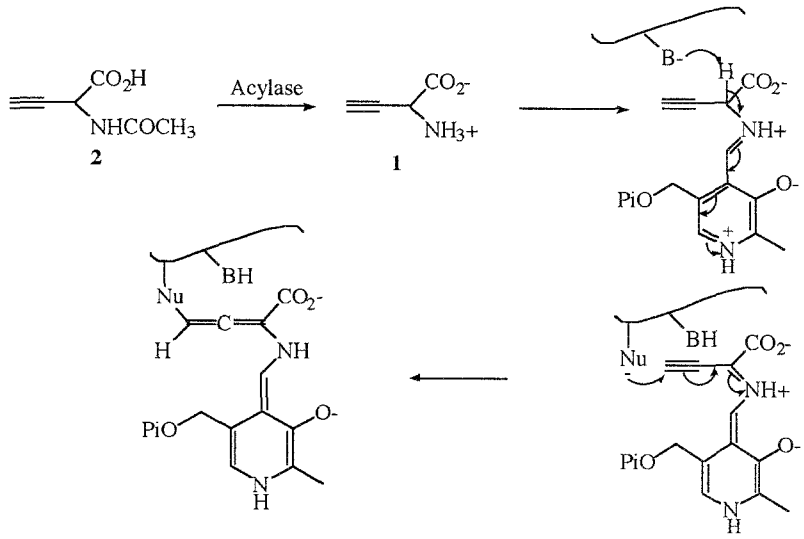


Fig. 1. Mechanism of inhibition according to Walsh

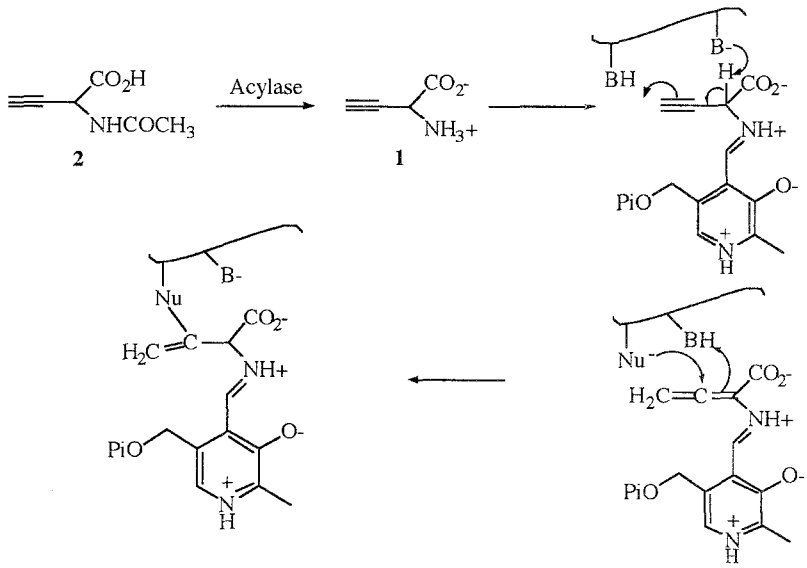


Fig. 2. Mechanism of inhibition according to Rando

Two possible mechanisms of inhibition of alanine racemase by ethynyl glycine **1** have been proposed and are depicted in Figs. 1 and 2 (Walsh, 1982; Rando, 1984) but these mechanisms have not yet been proven.

Therefore, it became evident and urgent for the organic chemist to find some general chemical syntheses of more stable derivatives of ethynyl glycine in order to be able to study their biological properties in more detail. This paper deals with strategies towards the synthesis of racemic and optically active β,γ-alkynyl α-amino acids described in the literature until now. It also shows and discusses advantages and limitations of each methodology.

2 Racemic syntheses of β,γ-alkynyl α-amino acids

The synthesis of racemic β,γ-alkynyl α-amino acids has already been reviewed as part of a more complete paper concerning the synthesis of β,γ-unsaturated α-amino acids (Havlicek and Hanus, 1991) and this part will complete and clarify some points.

β,γ-alkynyl α-amino acids have mainly been prepared in protected forms and have shown some obvious lability. Mostly, they have been synthesized as chemical intermediates, and none of them have been biologically studied.

In 1970, an acetylenic intermediate **5** was used in the synthesis of racemic diasteromers of phytosphingosine (Sisido et al., 1970). It was obtained from hydrazone **4** by a reductive amination as shown on Fig. 3.

Metcalf and Casara (Casara and Metcalf, 1978; Casara et al., 1978) used a coupling reaction between an electrophilic glycine **7** and bis (trimethylsilyl) acetylene **6** (Friedel-Crafts conditions) to synthesize a fully protected ethynyl glycine derivative **8** (Fig. 4). Unfortunately, the authors were not able to obtain free ethynyl glycine from compound **8** either in acidic or in alkaline conditions. Attempts to selectively split off the urethane group with $SiHCl_3$ lead to isomerization into an allenic isocyanate.

Fully protected analogues of compound **8** were used to synthesize α-acetylenic derivatives of α-amino acids (Casara et al., 1978; Danzin et al., 1981; Agouridas et al., 1990) with enzyme-activated inhibitor activity. These α-acetylenic α-amino acids are potent antibacterial agents.

The same authors have also described the synthesis of an analogous compound by the carboxylation of a protected propargylamine derivative **9**. An

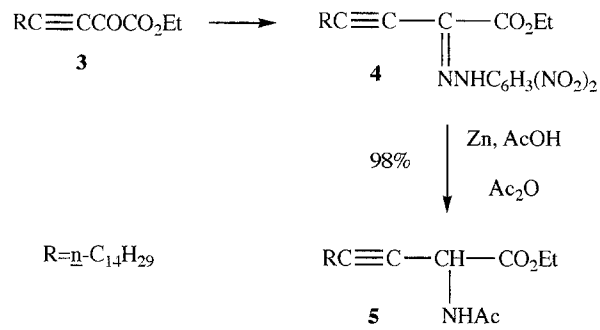


Fig. 3

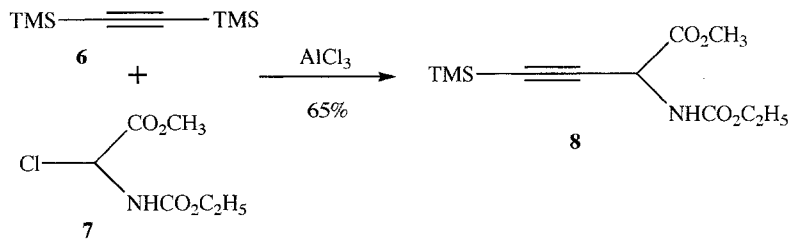


Fig. 4

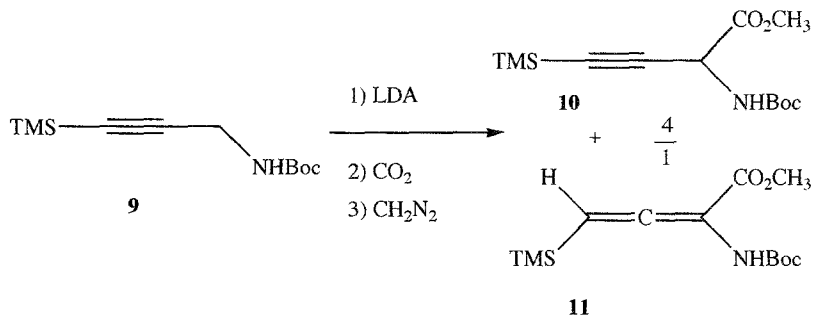


Fig. 5

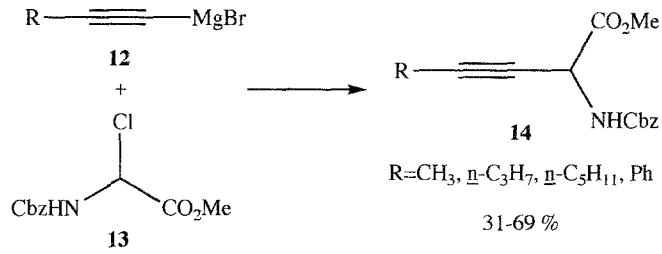


Fig. 6

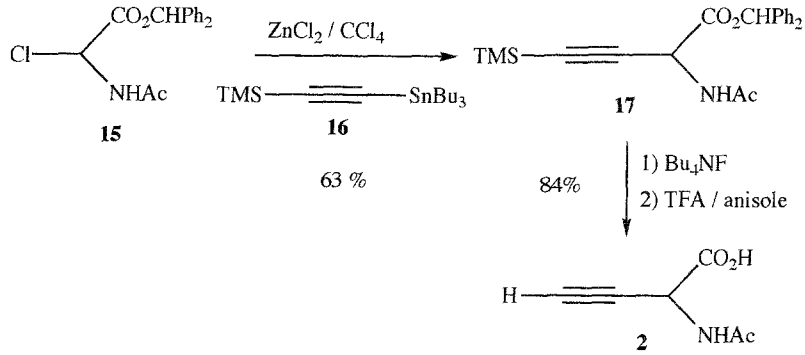


Fig. 7

allenic by-product **11** resulted on isomerization of the acetylenic compound **10** (Metcalf and Casara, 1979) (Fig. 5).

This methodology was patented and claimed the synthesis of α-acetylenic derivatives of α-amino acids useful as pharmacological agents (Metcalf and Jung, 1979; Metcalf and Jung, 1980).

In 1988, Castelhano and Krantz (Castelhano et al., 1988) reported a general synthesis of β,γ-unsaturated α-amino acids based on the condensation of Grignard reagents **12** on a glycine cation equivalent **13**. This methodology allowed to synthesize some protected β,γ-alkynyl α-amino acids **14** free from allenic products as shown in Fig. 6.

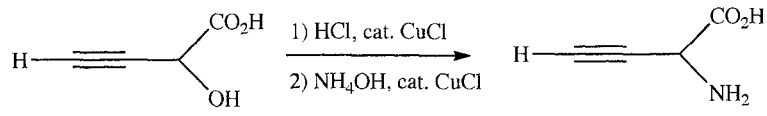
Williams et al. developed in 1988 (Williams et Zhai, 1988; Zhai et al., 1988) an alkylation method for electrophilic glycinates like **15** with trialkyltin

acetylides **16** followed by deprotection into N- or O-protected β,γ-alkynyl α-amino acid derivatives (Williams et al., 1990a). Despite large efforts, the free amino acids could not be isolated because of their instability.

In particular, racemic N-acetyl ethynyl glycine **2** was synthesized using this methodology as shown in Fig. 7 (Williams et al., 1990a, 1990b).

Three other patents claimed the synthesis of racemic ethynyl glycine derivatives via routes close to each other. The first one (Monroe et al., 1963) reported the synthesis of propargyl compounds, including ethynyl glycine **1**, as corrosion inhibitors according to Fig. 8. In view of the lability of this compound, it is unlikely that this procedure indeed yields compound **1**.

In the two other patents the synthesis of 2-amino-5-hydroxy-3-pentynoic acid **19** as an intermediate in the synthesis of adenosine derivatives is reported, according to Fig. 9 (Casara and Danzin, 1990; Bowlin, 1992). These compounds are claimed to be useful as S-adenosylmethionine decarboxylase inhibitors (inhibitors of cell growth proliferation, immunosuppressants).



18 **1**

Fig. 8

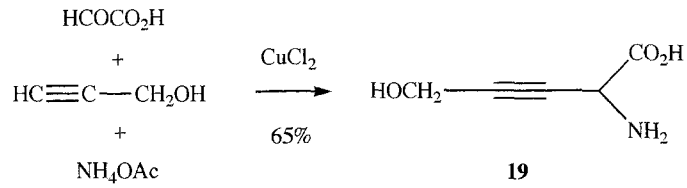


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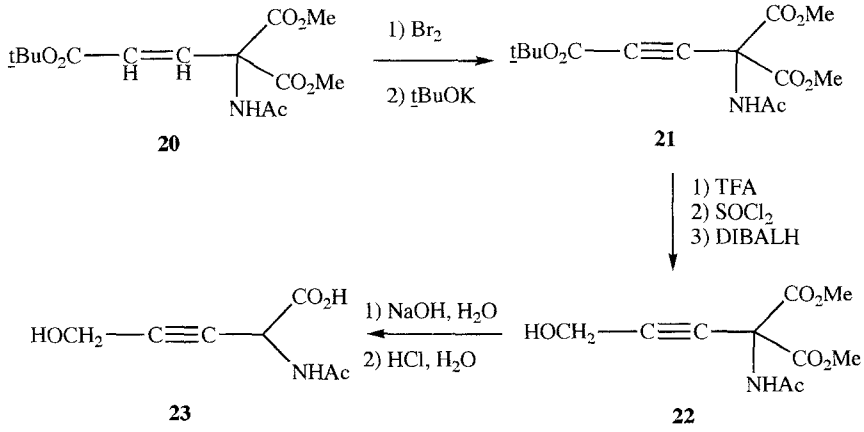
Fig. 9



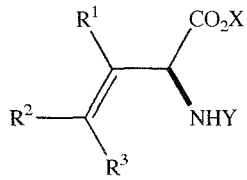
20 **21** **23** **22**

Fig. 10

Finally, Bowlin claimed in the same patent (Bowlin, 1992) the synthesis of compound **23** from acetamidomalonate derivative **20** using a classical strategy in amino acid synthesis as shown in Fig. 10.

3 Enantioselective synthesis of β,γ-alkynyl α-amino acids

Syntheses of optically active β,γ-alkenyl α-amino acids **24** are now well documented and a growing number of syntheses of that specific class of compounds including multifunctional side chains have been described (Duthaler, 1994; Havlicek and Hanus, 1991; Williams, 1989). β,γ-Alkynyl α-amino acid derivatives **25** are an extremely interesting and challenging class of unusual α-amino acids for which there was no suitable asymmetric synthesis until our recent papers (Meffre et al., 1995, 1996). Only racemic syntheses of protected **25** were described in the literature (see §2).



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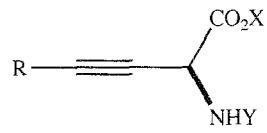

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Some methodologies applied to the synthesis of optically active compounds **24** could have also led to optically active compounds **25** but the presence of the alkyne function in **25** and its inherent reactivity made their synthesis more challenging.

The main problems caused by this small structure are the reactivities of amine, carboxylic acid or alkyne functions and the presence of the chiral center bearing the α proton between them which render this structure sensitive to acidic, basic, reductive and some oxidative conditions. Because of the increased acidity of the proton α to the triple bond, compared to amino acids possessing saturated side chains, this bond may isomerize into allene and the α carbon is prone to racemization.

Duthaler et al. (Duthaler and Hafner, 1994; Duthaler, 1994, 1992, 1991) used methodology where the thiomethylene group of cysteine is the precursor of the acid moiety via a Pummerer-type oxidation. In this methodology, L-cysteine gives rise to β,γ-unsaturated D-amino acids via thiazolidine aldehyde **26** (Fig. 11).

The $^1O_2$ – mediated C(5)-hydroperoxidation of **27** and **31** turned out to proceed very clearnly in the presence of sensitive functions including alkynes. The hydroperoxide **28** is therefore transformed into a thiolactone **29** from which the amino acid derivative **30** is obtained after treatment with LiOH, H_2O (**30**: 78% ee) or excess LiOH, H_2O_2 (**30**: >98% ee). Unfortunately rearrangement occurs in the transformation to the lactone in the case of the

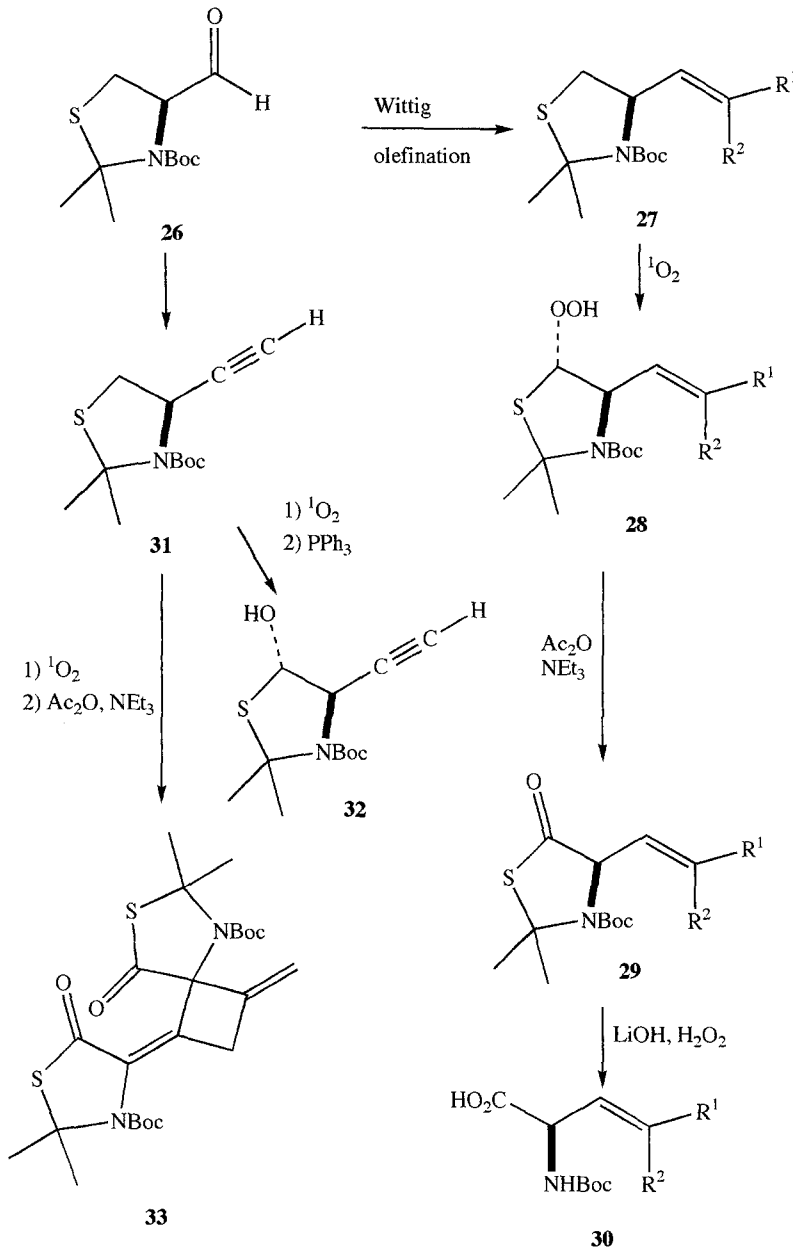


Fig. 11

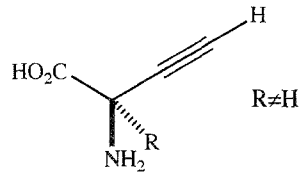
4-alkynyl compound **31** with isomerization into an allene and formation of dimer **33**. The same isomerization occurs in the case of the unbranched trans acrylic side chain compound **27** ($R^1 = CO_2CH_3$, $R^2 = H$) with formation of the α,β-unsaturated isomer.

To prevent these reactions indirect ways must be used as exemplified by the following results.

Williams et al. (Williams and Zhai, 1988; Zhai et al., 1988) use alkynylation of a chiral electrophylic glycinate **35** to obtain the optically active alkyne **36**. In this methodology, the amino acid moiety is already present when the

alkyne moiety is introduced. **34** represents a chiral glycine derivative. The pattern of the β,γ-alkynyl α-amino acid **25** in an optically pure form is present in **36**. N-Boc β,γ-alkenyl α-amino acids **37** are obtained in variable yield (Na°: 71–80%; Li°: 16–20%) and optical purity (Na°: 56–68% ee; Li°: 65–98% ee) after reductive cleavage of the heterocycle (Fig. 12). Nevertheless, the formation of isomerization products is not observed.

On the opposite, some methodologies succeeded in the synthesis of optically active α-alkyl α-ethynyl α-amino acid derivatives **38** (see for example: Colson and Megedus, 1993; Schöllkopf et al., 1988) where the absence of a proton in α-position protects the molecule from racemization, rearrangement or other ways of decomposition that penalize ethynyl glycine (and vinyl glycine) derivatives.



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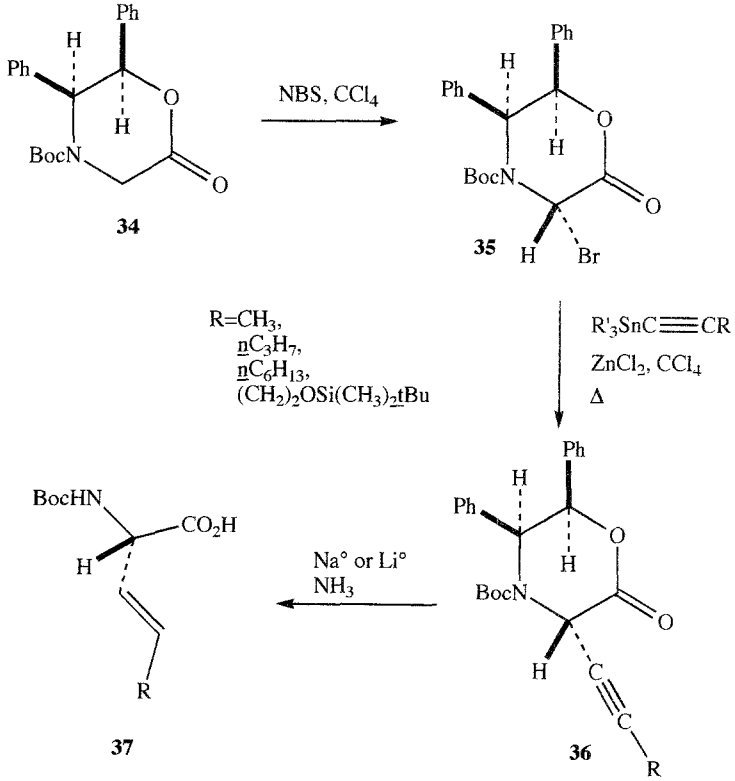


Fig. 12

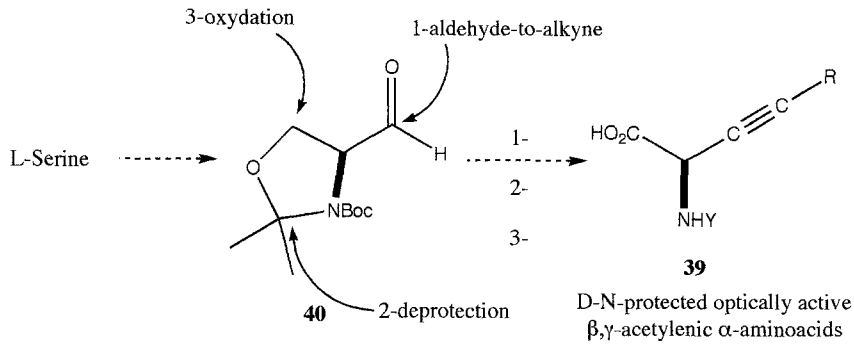


Fig. 13

Recently, we reported the first synthesis of optically active ethynyl glycine derivatives (Meffre et al., 1995, 1996). Stable D-configured N-protected β,γ-alkynyl α-amino acids **39** were synthesized from L-serine according to the methodology shown in Fig. 13.

This methodology has several advantages:

1. L-Serinal **40** is a configurationally stable formylglycine (penaldic acid) equivalent, even under strongly basic or nucleophilic conditions (Wittig olefination, Grignard, Reformatzki, ...). This intermediate is now commercially available and the large scale preparation from L-serine is well documented (Meffre et al., 1994; Branquet et al., 1993; Garner and Park, 1992, 1987; Garner, 1984). It has already been used in numerous syntheses of unusual amino acids including optically active β,γ-alkenyl α-amino acids (Duthaler, 1994; Williams, 1989).
2. Many synthetic transformations are available to convert an aldehyde into a terminal alkyne, and a terminal alkyne into a substituted one.
3. Unmasking the primary alcohol function could be foreseen with concomitant introduction of various N-protecting groups because oxazolidine and Boc groups could be cleaved under the same conditions.
4. The principal methods to convert a primary amino alcohol into an amino acid (i.e. Cr^{VI}-based reagents, Pt/O_2) are reported to be compatible with unsaturated side chains including triple bonds, although others methods could be used as well.

The full sequence we have developed is outlined in Fig. 14.

Among the methods allowing the transformation of an aldehyde into an alkyne, the protocol reported by Ohira (Ohira, 1989) using dimethyl 1-diazo-2-oxopropyl phosphonate **41** worked very well and allowed an easy, clean and large scale one-step synthesis of optically pure alkyne **42a** from aldehyde **40** with a very good yield.

The transformations of the terminal alkyne **42a** into the substituted derivatives **42b–d** were performed using alkynide formation with BuLi followed by trapping with the adequate electrophile.

Some other 4-alkynyl-oxazolidine derivatives of the same type as **42** have recently been reported (Reginato et al., 1995). Compounds **42** are obviously interesting highly functionalized chiral intermediates.

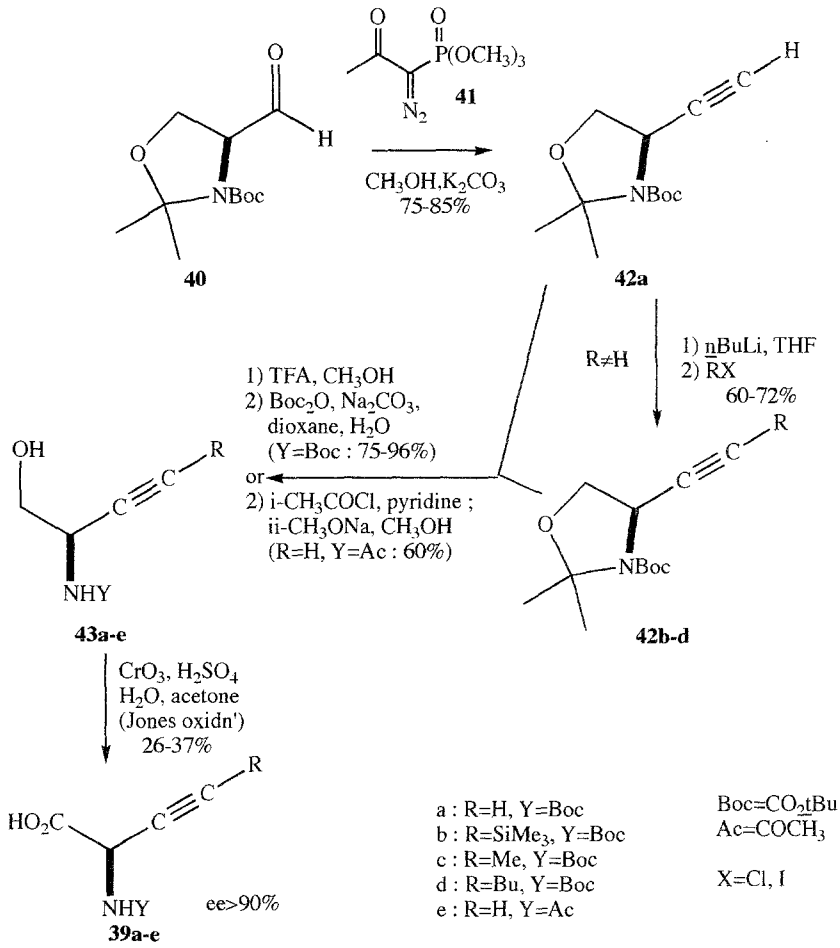
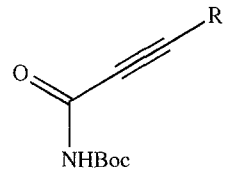


Fig. 14

Transformation of the oxazolidines **42** into the alcohols **43** was best performed by simultaneous Boc and oxazolidine ring solvolysis (Stanley, 1992) followed by reprotection by Boc or acetyl in good yield.

The final oxidation step proved to be very challenging because of the lability of the transient aldehydes and of the final products. Those compounds possess a triple bond in the β,γ-position that could react under some oxidative conditions and degradation is highly likely with different oxidative procedures (Haines, 1985, 1988). Moreover, they can also form a conjugated enol and allene. Some methods that are compatible with unsaturations have been tried {PDC/DMF (Beaulieu, 1991); Pt, O_2 (Mehmandoust et al., 1992) among others} but failed or resulted in degradation. However, it is known that oxidation of primary acetylenic alcohols proceeds with variable yields and Jones oxidation is generally the best method in such cases (Haines, 1988; Cainelli and Cardillo, 1984). N-Boc alkynyl amino acids **39a–d** were indeed best synthesized using Jones oxidation under reverse and slow addition method (Manfré et al., 1992; Holland and Gilman, 1974) with yields between 26% and 37% in a reproducible way. Unsaturated carbamic esters **44** were also isolated during this step in yields between 11% and 24% due to C—C

bond cleavage. This phenomenon is known to occur quite often in chromium-VI based oxidation, particularly with enolizable aldehydes (Bijoy and Subba-Rao, 1993; Li and Johnson, 1995). A mild acid base work-up allowed separation and isolation of major N-Boc amino acids **39a–d** and carbamic esters **44a–d**. It is noteworthy that substitution of the triple bond with alkyl groups has no determining effect on the proportion of cleavage products **44**.



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In the case of N-acetylated derivatives **43e** a low yield (ca. 30%) of a mixture containing a high proportion of **44e** is obtained whose separation from **39e** could not be performed.

The enantiomeric excess (ee) of starting serinal **40** is >90% as verified by ^{19}F NMR analysis (variable temperature) on Mosher's esters derivatives (Mosher, 1973) and confirmed by optical rotation (Meffre et al., 1994). The enantiomeric excess (ee) of the final products was measured after derivatization to known saturated N-Boc α-amino methyl esters **45** (shown in Fig. 15) by chiral capillary GC analysis. The ee values proved to be 91–93%. Moreover, the optical rotation indices of compounds **45** are in good agreement with the literature and/or authentic samples, and confirm the absolute configuration of **39** to be (*R*).

Optically active (*R*)-N-Boc β,γ-alkynyl α-amino acids are synthesized with ee >90% in only 3 or 4 steps with no racemization from L-serinal. The optically active precursors, the protected 2-amino-3-alkyn-1-ols, are obtained in good overall yields. The strategy allows versatility on amino protecting group (N-Boc protection seems to be the best so far) and on the alkyne substitution. The best way to perform the last oxidation step is the Jones oxidation although significant C-C bond cleavage is observed. Considering the examples studied, the influence of the alkyne substitution on the outcome of the oxidation or on the enantiomeric stability of final products is not a decisive factor.

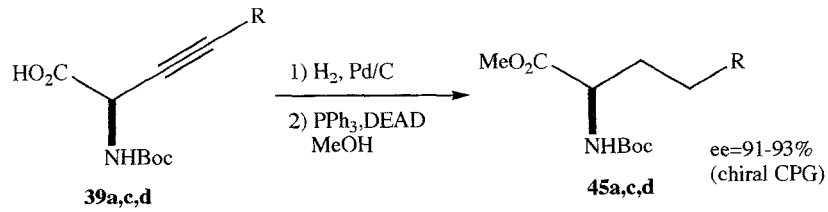

Fig. 15

This method is the first satisfactory synthesis of optically active N-protected β,γ-alkynyl α-amino acids until now and has to be developed and improved to lead to biological evaluation.

Concluding remarks

The results presented in this paper provide evidence that the synthesis of β,γ-alkynyl α-amino acids in general and particularly in optically active form represents a real synthetic challenge due to the number, the proximity and the reactivity of all the functions present in such small polyfunctional structures. A few satisfactory methods are appropriate to synthesize racemic β,γ-alkynyl α-amino acids and only one is able to obtain optically active compounds, totally or partially protected on the carboxyl, amino or alkyne functions. The choice of the protecting groups, (optically active) stable intermediates and reaction conditions are crucial, especially in that type of small labile compounds. Anyway, trying to synthesize and isolate unprotected β,γ-alkynyl α-amino acids would not be realistic if we consider the problems encountered by the groups involved in their synthesis.

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Authors' address: Dr. P. Meffre, Laboratoire de Bioorganique et Biotechnologies, E.N.S.C.P., 11 rue P. et M. Curie, F-75231 Paris Cédex 05, France.

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