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Synthesis of Optically Active β,γ-Alkynylglycine Derivatives[1]

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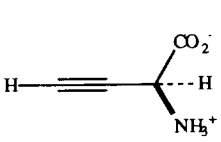
Abstract : Full results on the first synthesis of optically active β,γ-alkynylglycine derivatives from naturally occurring L-serine are described. The methodology uses L-serinal as a key intermediate and allows great versatility in the introduction of N-protective groups and of alkyne substitution. The N-Boc protected β,γ-alkynylglycine derivatives described have ee greater than 90%. Copyright © 1996 Elsevier Science Ltd

The β,γ-unsaturated α-aminoacids have attracted much attention in recent literature especially because it is now recognized that compounds bearing α-ethynyl and α-vinyl substituents are constrained α-aminoacid analogues with potential mechanism-based inactivating properties of specific target enzymes. They can therefore profoundly alter metabolism and especially that of microorganisms.[2]

The simple α-ethynyl-α-aminoacid **1** is a secondary metabolite and has been characterized as its N-acetyl derivative with L-configuration. It displays antimicrobial activity against gram-positive bacteria and acts synergistically with D-cycloserine. Its biological properties could be explained by its inhibitory activity on L-alanine racemase, a PLP dependant enzyme. This notoriously labile compound is obtained from a culture of *Streptomyces Catenulae* as a hygroscopic 70% pure powder in a very low yield.[3]



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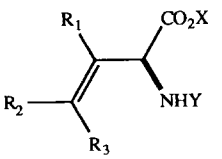

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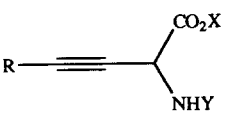


3

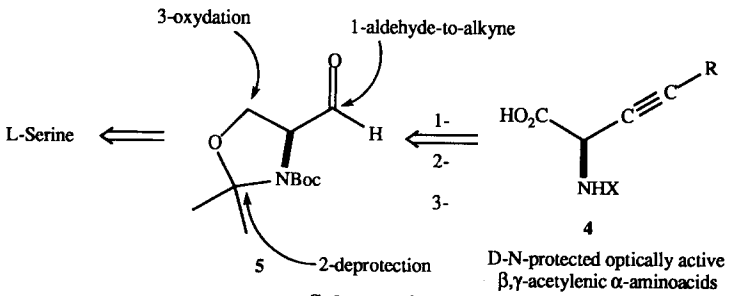
Preparation of optically active β,γ-ethylenic α-aminoacids **2** are now well documented and a growing number of synthetic approaches of that specific class of compounds including multifunctionnal side chains have been described.[4] An extremely interesting and challenging class of unusual α-aminoacids, for which there was no suitable asymmetric synthetic solution until our recent communication[5], are the β,γ-acetylenic α-aminoacids **3**, although racemic syntheses of protected **3**[2e,4b,4c,6] have been described in the literature. Some methodologies applied for the

synthesis of optically active **2** could have also led to optically active **3** but the presence of the alkyne function in **3** and its inherent reactivity made their synthesis more challenging[4c,7].

The main problems caused by this small structure are due to the reactivity of amine, carboxylic acid or alkyne functions and the stereogenic center between them which renders this structure sensitive to acidic, basic, reductive and some oxidative conditions. Because of increased acidity of the proton α to the triple bond (compared to amino acids bearing saturated side chains), it may isomerize into allene or racemize.

We have been working for a long time on the chemistry of β,γ-unsaturated α-aminoacids[8] and have recently reported that N-Boc-D-ethynylglycine can be obtained in an optically active form from L-serine.[5] In the present paper we wish to report full results concerning the synthesis of D-N-protected optically active β,γ-acetylenic α-aminoacids **4** from this α-aminoacid.

L-serinal **5**, a configurationnaly stable formylglycine (penaldic acid) equivalent, was selected as chiral building block. This intermediate is now commercially available and large scale preparation from L-serine is well documented.[9] It has already been used in numerous syntheses of unusual aminoacids including β,γ-ethylenic α-aminoacids.[4a,4c]



Scheme 1

The retrosynthetic pathway we have followed is outlined in **Scheme 1** and has several advantages :

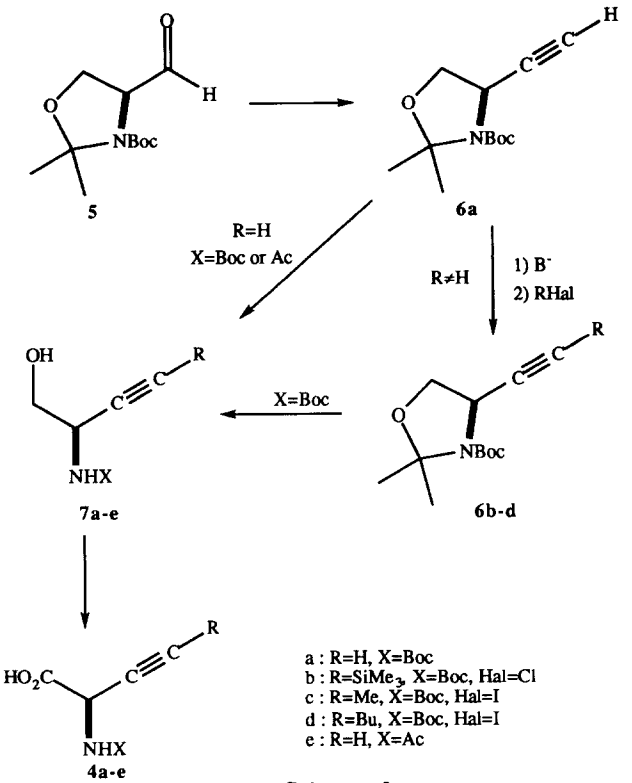
1-Serinal **5** is a configurationally stable intermediate even under strongly basic or nucleophilic conditions (Wittig olefination, Grignard, Reformatski, ...)[4,9] and both enantiomers are available.

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 forseen 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 aminoalcohol into an amino acid (i. e. Cr^{VI} -based reagents, Pt/O_2) are reported to be compatible with unsaturations including triple bond, although other methods could be used as well.

The full sequence we have developed is outlined in **Scheme 2.**



Scheme 2

Synthesis of the 4-alkynyl-1,3-oxazolidines **6**

Parent 4-ethynyl-1,3-oxazolidine **6a** was first synthesized from aldehyde **5**.

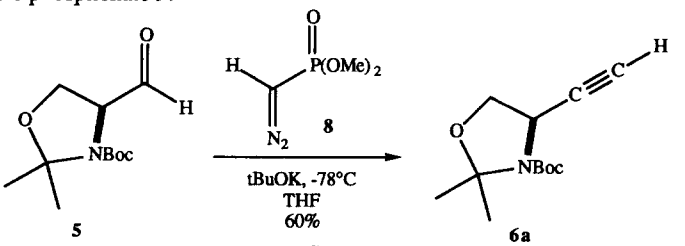
a-Synthesis of alkyne **6a** from aldehyde **5**

The well-known and frequently used Corey-Fuchs method[10] was first tried but led in our hands to numerous by-products and thereby low yields of **6a**.[10b] Although widely used, the original two step procedure *via* dibromovinyl intermediates followed by BuLi halogen-metal exchange and elimination suffers from serious drawbacks when applied to highly functionnalized and/or sensitive aldehydes and prompted improvements of this procedure.[11] Recently published results have demonstrated the usefulness of this reaction when working at low temperature.[10c]

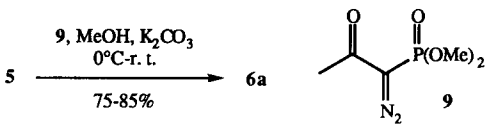
We therefore turned to a more direct and milder method using diazomethyl phosphonates as ethynyl donors.[12] This approach has been successfully used to obtain without racemization chiral propargylic amines from protected α-amino aldehydes.[13]

In fact, Gilbert's method[12] worked quite well (**Scheme 3**). Dimethyl diazomethyl phosphonate **8** was found however to be tricky to synthesize and to purify, as described in the literature[14] (multiple steps, low overall yield, sensitive reagent). We therefore examined the

modified method described by Ohira[15] which worked nicely as shown in **Scheme 4**, with an easily accessible phosphonate **9**.



Scheme 3



Scheme 4

Dimethyl-1-diazo-2-oxopropyl phosphonate **9** is indeed readily synthesized and purified by flash chromatography in good yield on large scale from tosylazide and commercially available dimethyl-2-oxopropyl phosphonate.[15b]

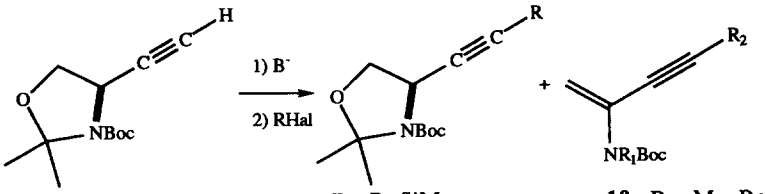
This method allows the easy, clean and large scale one-step synthesis of optically pure alkyne **6a** from aldehyde **5** in high yield.[16]

b-Synthesis of substituted alkynes **6b-d**

In order to obtain more stable analogues of ethynylglycine as well as a series of molecules with more potent and broaden biological properties, we first decided to introduce substituents on the triple bond. Trimethylsilyl moiety was introduced because it is a protecting group removable later to obtain free N-protected ethynylglycine. This strategy has already been used previously by Williams *et al.* in the synthesis of racemic N-acetyl ethynylglycine.[6a,b]

Beaulieu *et al.*[17] reported in their stereoselective synthesis of vinylglycines using the same strategy, that the final oxidation step of the alcohol into the acid did not occur when the double bond is substituted with electron withdrawing groups like phenyl or methoxycarbonyl. Duthaler *et al.*[7d,7e] were faced to the same problem in their stereoselective synthesis of vinylglycines. During their $^1O_2$ oxidation at the same position of thiazolidine derivatives with unbranched acrylic side chains, double bond migration occured from β,γ to α,β position whereas isomerization was prevented with double bond branching. Moreover, alkyl substituent on the triple bond would prevent from isomerization and racemization because of the decreased acidity of the α proton. Therefore, methyl and butyl substituents were introduced.[7a]

Acidity of acetylenic proton in **6a** allows easy functionalization at this position as shown in **Scheme 5** and **Table I** (see also ref.10c).



6a

6b : R=SiMe3
6c : R=Me
6d : R=Bu

10 : R_1=Me, R_2=H
11 : R_1=R_2=Me
12 : R_1=R_2=Bu

Scheme 5

entry	RHal	experimental conditions	isolated products (yield)	
1	TMSCl	1)BuLi : 1.1 eq. ; THF, -70°C 2)TMSCl : 1.2 eq..; -70°C-rt, 24hr	**6b** (60%)	
2	MeI	1)BuLi : 1.1 eq. ; THF, -70°C 2)MeI : 3 eq..; -70°C-rt, 15hr	**6c** (45%)	**11** (25%)
3	MeI	1) BuLi : 1.1 eq., HMPA, 0°C 2) MeI : 1.1 eq..; 0°C ; HMPA	{**10** (major)+**11**} (16%)	
4	MeI	1)BuLi : 1.1 eq. ; THF, -70°C 2)MeI : 1.1 eq..; HMPA,-70°C-rt, 15hr	{**6a** +**6c**} (53%) (**6c**/**6a**=2.8/1)	**11** (8%)
5	MeI	1)BuLi : 1.1 eq. ; THF, -70°C 2)MeI : 3 eq..; -70°C-rt, 3.5hr	{**6a** +**6c**} (65%) {**6c**/**6a**=5.5/1}	**11** (4%)
6	MeI	1)LDA : 1.1 eq. ; THF, -70°C 2)MeI : 3 eq..; -70°C-rt, 15hr	{**6a** +**6c**} (69%) (**6c**/**6a**=13/1)	
7	MeI	1)LDA : 1.2 eq. ; THF, -70°C 2)MeI : 3 eq..; -70°C-rt, 15hr	{**6a** +**6c**} (53%) {**6c**/**6a**=17/1}	**11** (10%)
8	MeI	1)BuLi : 1.1 eq. *(freshly opened)* THF, -70°C 2)MeI : 3 eq..; -70°C-rt, 15hr	**6c** (72%)	**11** (10%)
9	BuI	1)BuLi : 1.1 eq. *(freshly opened)* THF, -70°C 2)BuI : 3 eq..; -70°C-rt, 15hr	**6d** (70%)	**12** (<10%)

Table I

Several different reaction conditions have been examined and the formation of enamines **10-12** have been observed in some cases[10b,18]. Results are reported in **Table I.**

Trimethylsilyl (TMS) substitution occurred easily using the standard procedure (entry 1).

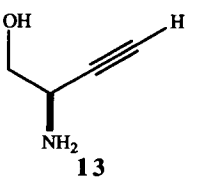
In the case of methylation (entries 2-8), experimental conditions have been set up in order to complete the consumption of starting material **6a** because **6c** is not separable from **6a** by silica gel

chromatography. Under similar conditions as with TMSCl, **6c** was formed in moderate yield, even in the presence of an excess of MeI (entry 2). In the presence of HMPA as co-solvent, the formation of enamines and degradation products (entry 3) or uncompletion of reaction (entry 4) were observed. A shorter reaction time decreased the amount of by-product **11** but with concomitant incompleted reaction (entry 5). We tried therefore to minimize formation of enamines **10** and **11** by using lithium diisopropylamide (LDA) but noticed that complete consumption of starting material was not possible even when **11** was formed significantly (entries 6, 7). Finally and unexpectedly, a good yield in **6c** (and **6d**) was obtained when a freshly opened BuLi bottle was used (entry 8 and 9).

Synthesis of the N-protected (2R)-2-amino-3-alkyn-1-ols **7**

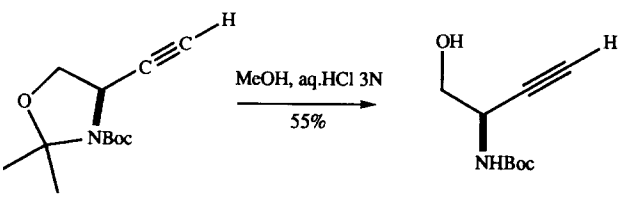
Synthesis of N-Boc derivatives **7a-d**

Optimal reaction conditions were searched with **6a** as starting material. A lot of different methods have been described in the literature to selectively cleave oxazolidine ring on similar compounds (directly to the N-Boc aminoalcohol) : MeOH, APTS, r.t.[19] ; $CHCl_3$, camphor sulfonic acid, Δ[20] ; Amberlist 15, MeOH[21] ; DOWEX 50WX8, MeOH[17]. As already reported[22], this transformation proved to be problematic in our case too, leading to the recovery of starting material and/or degradation into the unstable fully deprotected acetylenic aminoalcohol **13**.[23]



13

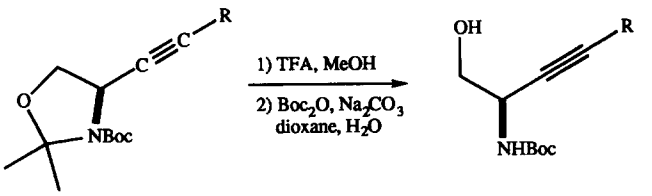
Best yields of **7a** (*ca.* 55%) were obtained with MeOH, aq. HCl 3N at r.t.[24] (**Scheme 6**).



6a **7a**

Scheme 6

We therefore used the method reported by Stanley[22a] : simultaneous Boc cleavage and oxazolidine hydrolysis using TFA in water followed by reprotection with di-*tert*-butyl dicarbonate without isolating **13** gave **7a** in 65% to 85% yields. Finally, the use of methanol in the solvolytic step[25] led to 75% to 90% yields. Complete results of the conversion of **6a-d** into **7a-d** are reported in **Scheme 7**.

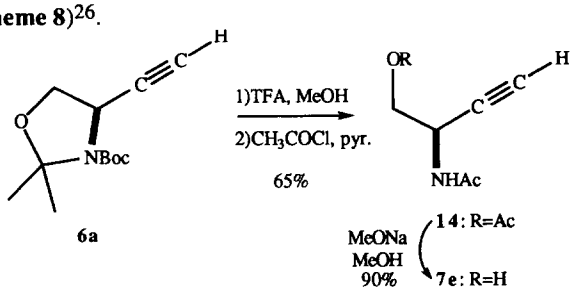


6a : R=H	**7a** : R=H	90%
6b : R=SiMe3	**7b** : R=SiMe3	96%
6c : R=Me	**7c** : R=Me	75%
6d : R=Bu	**7d** : R=Bu	87%

Scheme 7

Synthesis of N-Acetyl derivative **7e**

The above strategy, *via* N-unprotected homopropargylic alcohol **13**, allowed us to change the amino protecting group at this stage. In order to obtain the enantiomer of the N-acetylated natural ethynylglycine[3], we transformed **6a** into the N-acetylated aminoalcohol **7e** *via* the *N,O*-diacetylated compound **14** (**Scheme 8**)[26].



Scheme 8

Synthesis of the N-protected (2R)-2-amino-3-alkynoic acids **4**.
(N-protected D-alkynylglycines)

The oxidation of the N-protected aminoalcohols **7** into the N-protected D-alkynylglycines **4** proved to be the most challenging step, because of the lability of the intermediate aldehydes and of the final products. These compounds possess a triple bond in the β,γ-position and the propensity to form conjugated enol and allene, among other possibilities is highly likely.

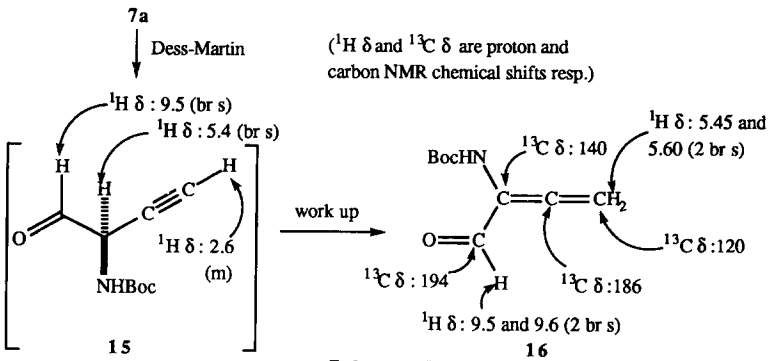
Various methods have been used for the conversion of primary alcohols into the corresponding carboxylic acids[27a] but very few are compatible with the presence of unsaturated bonds. For example ruthenate anion-based oxidation[4a,17,27,28], permanganate anion-based oxidation[4a,17,22c,27], nitric acid[27a], electrochemical oxidation[27a,29] at a nickel hydroxide anode are not suitable for a substrate bearing a triple bond, which could react in such conditions. Marginal method like Nickel peroxide in alkaline aqueous solution[30] is also not possible. Two-steps oxidations like Me_2S, N-chlorosuccinimide followed by $NaClO_2$[31] ; Swern oxidation followed by $NaClO_2$[32] or acetone cyanohydrine or pyridinium chlorochromate (PCC)/NaCN[33] or, finally but

not exhaustively, pyridinium dichromate (PDC) in dichloromethane followed by PDC in DMF/MeOH[34] *via* highly unstable propargylic α-amino aldehyde **15** are not recommended for such substrates.

The preliminary studies were performed on alcohol **7a**. Indeed, all the attempts to isolate aldehyde **15** from alcohol **7a** (Swern oxidation, Pfitzner-Moffat with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI)[35,36]) led to the degradation and the isolation of unidentified products. Neutral Dess-Martin oxidation[37] of **7a** led presumably to allene **16** after work up *via* aldehyde **15** which formation was observed by ^{1}H NMR (**Scheme 9**).

The methods already reported to form some N-protected β,γ-unsaturated α-aminoacids from the primary unsaturated alcohols are Pt/O_2[38], PDC in DMF[17,39] and Jones oxidation[17,40]. The first method is reported to be sluggish[4a] and we indeed observed a very slow evolution. The second one is known to be problematic due to the difficulty in the isolation of final product (separation of chromium salts). We observed degradation and formation of unidentified products.

Results of our preliminary observations are reported in **Table II**.



Scheme 9

Reaction conditions	Results
Dess-Martin[37]	Formation of **16**
PCC, NaCN[33]	Recovery of Starting material.
Swern[35]	Degradation.
Pfitzner-Moffat (EDCI)[36]	Degradation.
TEMPO, $NaClO_2$[41]	Recovery of Starting material.
Pt/O_2[38]	Very slow evolution. Degradation during work up.
PDC/DMF[17]	Degradation.

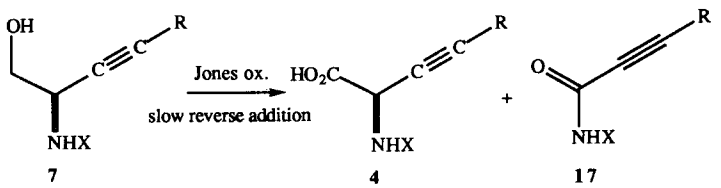
Table II

Oxidation of alcohols 7 into acids 4 using Jones oxidation

It is known that oxidation of primary acetylenic alcohols proceeds with variable yields and Jones oxidation is generally the best method in such cases.[27]

Literature shows that Jones oxidation is compatible with alkynic functionalities[27a,42,43], although yields are sometimes low. Standard Jones oxidation (Jones reagent added to the alcohol)[17,42a-f] proved to be unreliable and unreproducible in our case.

Ultimately, Jones oxidation under reverse[42g,h] and slow addition conditions allows reproducible formation of N-protected 2-amino-3-alkynoic acids **4** together with unsaturated imides **17** (**Scheme 10**). Results are reported in **Table III**.



7 **4** **17**

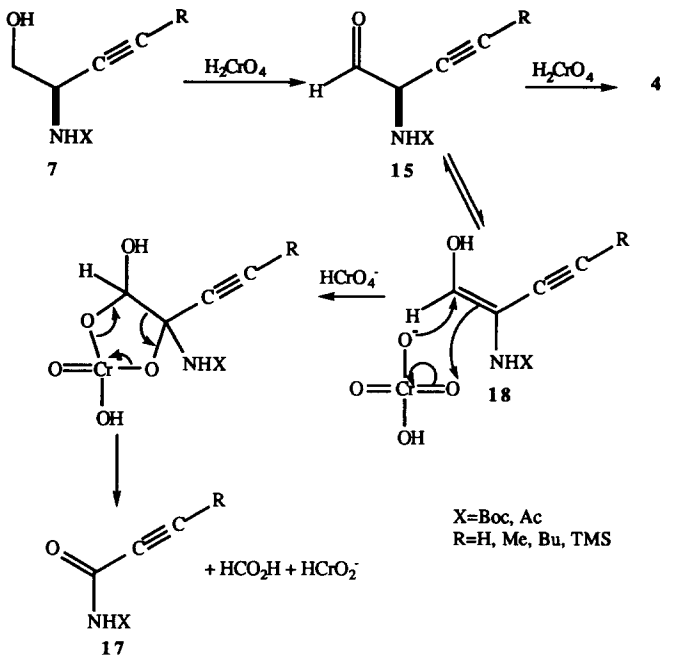
Scheme 10

alcohol **7**	yield[a] of **4**	**4** : $[\alpha]_D^{20}$	yield[a] of **17**
7a (X=Boc, R=H)	**4a** : 32%	-53.9 (c=0.89, $CHCl_3$)	**17a** : 22%
7b (X=Boc, R=$SiMe_3$)	**4b** : 33%	-60.8 (c=1.15, $CHCl_3$)	**17b** : 23%
7c (X=Boc, R=Me)	**4c** : 26%	-46.0 (c=1.10, $CHCl_3$)	**17c** : 24%
7d (X=Boc, R=Bu)	**4d** : 37%	-8.0 (c=1.01, $CHCl_3$)	**17d** : 11%
7e (X=Ac, R=H)	*ca.* 30%[b]		

a-isolated yields after mild work up (see experimental part).
b-yield after filtration, evaporation of acetone, addition of water, extraction with EtOAc and drying over Na_2SO_4.
RMN ^1H analysis shows the following proportions : **17e/4e/7e**= 3.5/1/0.8

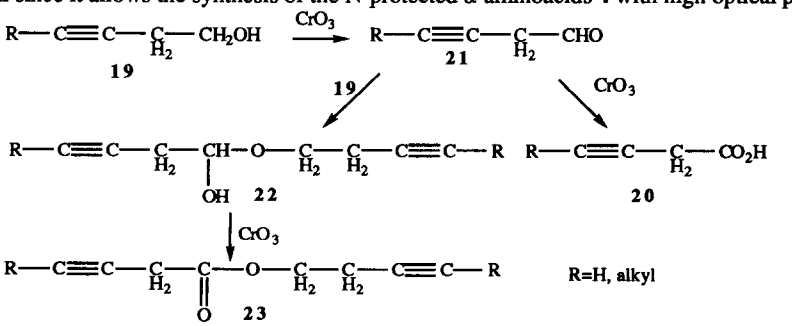
Table III

Formation of by-products **17** is due to C-C bond cleavage and is known to occur frequently in chromium-VI-based reagents (collins reagents, PDC or PCC), particularly in the case of enolizable aldehydes[44a-c,e]. A possible mechanism is depicted in **Scheme 11** (see also lit.[43b,44d]). In the case of Boc derivatives **7a-d**, a mild work up (see experimental part) allows the separation and the isolation of major **4a-d** and **17a-d**. In the case of the N-acetylated aminoalcohol **7e**, a low yield of a mixture containing a high proportion of **17e** is obtained, but separation from **4e** is not possible. It is worth noting that substitution of the triple bond with alkyl groups has no determining effect on the formation of cleavage products since, as shown by NMR analysis of the crude reaction mixture, the **4a-d/17a-d** ratio varies usually between 1/1 and 1.5/1. This is confirmed by the yields of isolated products **4a-d** and **17a-d**, in all cases studied so far.



Scheme 11

Formation of chromium species with intermediate valence (Cr^{IV}, Cr^{V}) has also been advanced to explain such a cleavage[43] but adding scavengers such as $Mn^{II}(NO_3)_2$ had no effect on the course of the reaction in our hands. Reverse addition in Jones oxidation (alcohol added to Jones reagent) was introduced in Jones oxidation of primary alkynols of type **19** into acids **20** in order to prevent the formation of the esters **23** *via* the hemiacetals **22**[42h] (**Scheme 12**). In our case, since the alcohols **7** are added *dropwise to* Jones reagent, **7** and the intermediate aldehydes **15** are always in the presence of an excess of the oxidant and are therefore quickly converted into acids **4**, which lowers degradation. Moreover, the racemization products due to the enolization of **15** into **18** would not be present because the latter react with chromic acid to form imides **17**, easily separated from acids **4**. Problematic at first, the formation of these by-products is actually beneficial since it allows the synthesis of the N-protected α-aminoacids **4** with high optical purity.

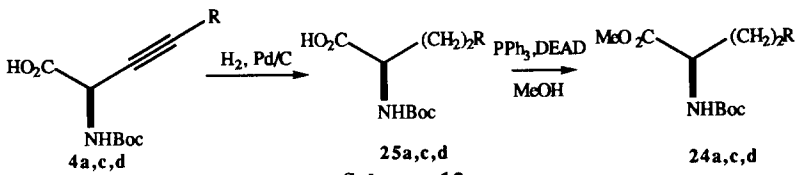


Scheme 12[42h]

Determination of enantiomeric excesses.

Enantiomeric excess (ee) of serinal **5** is >90%[9]. Enantiomeric purity of alcohol **7a**, precursor of N-Boc-D-ethynylglycine **4a** was checked by derivatization to Mosher's esters[45] with (S)-(+)- and (R)-(-)-α-methoxy-α-(trifluoromethyl) benzene acetyl chloride followed by ^{1}H and ^{19}F NMR analysis. The ee proved to be >90%.

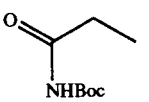
The ee of final products **4** were measured after derivatization to known saturated N-Boc α-amino methyl esters **24** *via* formation of the saturated acids **25** as shown in **Scheme 13**.



Scheme 13

Chiral GC analysis of **24a,c,d** showed the ee to be higher than 90% (**Table IV**). Moreover, optical rotation values of compounds **24** obtained from **4** as shown in **Scheme 13** are in good agreement with the literature and/or authentic samples, and confirm the D configuration of **4**. We assume that the optical rotation discrepancy for **24c** is not significant and does not reflect a loss in optical purity since the chiral GC analysis confirms the ee value to be >90%.

Derivatization of **4c,d** into **24c,d** was performed starting from pure **4c,d**, obtained after mild work up, while **24a** was synthesized starting from crude **4a** containing the imide **17a** (see **Scheme 10** and **Table III**). In the latter case, **26**[47] was obtained as well, which confirms the structure of **17a**.



26

24[a]	ee (%)[a]	$[\alpha]_D^{20}$(config.[a]) observed[b]	$[\alpha]_D^{20}$(config.) literature[c]	$[\alpha]_D^{20}$(config.) synthesized[d]
24a (R=H)	93	+31.7 (D) (c=2.3, MeOH)	-39 (L) (c=2, MeOH)	-33 (L) (c=2.3, MeOH)
24c (R=Me)	91	+15.2 (D) (c=1.1, EtOH)	+32 (D) (c=1, EtOH)	+28.2 (D) (c=2.2, EtOH)
24d (R=Bu)	91	+16.3 (D) (c=2.1, MeOH)	-18 (L) (c=2.6, MeOH)	-

[a] Co-injections with authentic samples D-, L-, and/or D,L-**24** whenever available have been performed for confirmation of peaks attribution (see Experimental). No standard was available for **24b**.

[b] **24** obtained as shown in **Scheme 13**.

[c] **24a**[46a] ; **24c**[46b] ; **24d**[46a].

[d] **24** synthesized from commercially available D and /or L saturated α-aminoacids using standard protocols.

Table IV

In conclusion, we describe here the first synthesis of optically active (R)-N-protected-β,γ-acetylenic α-aminoacids with ee>90% in only 3 or 4 steps from L-serinal with no racemization. Optically active N-protected 2-amino-3-alkyn-1-ols, direct precursors of the optically active alkynyl glycine derivatives, are obtained in 2 or 3 steps in good overall yields. Our strategy allows versatility on amino protecting groups and on the substitution of the alkyne group. These acetylenic protected amino alcohols are obviously valuable chiral intermediates.[10c,d] The best way to perform the last oxidation step is the Jones oxidation although significant C-C bond cleavage is observed, for which a mechanism is proposed. N-Boc protection seems to be the best so far and isolation of optically active N-protected-β,γ-acetylenic α-aminoacids with D configuration is possible after a mild work up. Influence of the substitution on the triple bond is not clear so far neither on the formation of cleavage products nor on the enantiomeric stability of the N-Boc aminoacids. Biological evaluation of final products are under investigation in our laboratory.

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EXPERIMENTAL

General Methods.

Commercial BuLi solutions were extemporaneously titrated according to the Suffert's method[48] and tetrahydrofuran freshly distilled from sodium / benzophenone ketyl prior to use.

Unless otherwise stated, ^{1}H NMR and ^{13}C NMR spectra were recorded on a 200 MHz Brucker at room temperature using chloroform-*d* as solvent. Chemical shifts (δ) are given in parts per million (ppm) downfield from tetramethylsilane and coupling constants (J) in Hz. The following abbreviations are used : s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, br=broad. In these conditions, oxazolidines (**5**, **6**) as well as N-Boc α-aminoacids (**4**, **25**) exist as slowly interconverting rotamers which explains that some signals are split or broad. Heating samples is necessary to obtain averaged spectra. Temperature NMR experiments were performed on compound **4a** (and on the corresponding saturated derivative **25a**) allowing us to say that **4** are obtained as single pure compounds after work up. Moreover, N-Boc-D-ethynylglycine **4a** isolated after mild work up was purified by preparative HPLC using Delta pak column Waters C18, 100Å, 15μ, flow rate : 20ml/min., eluent : water / acetonitrile = 85/15. It did not increase chemical and optical purity significantly.

Melting points were measured using a Mettler FP 61 apparatus. IR spectra were obtained on Nicolet IRFT 205 spectrophotometer and wave-numbers of characteristic absorption bands are

given in cm^{-1}. Optical rotations were measured using a Perkin Elmer Model 241 polarimeter using chloroform as solvent unless otherwise specified. Elemental analyses were performed by the "Service de Microanalyse", ICSN/CNRS, Gif sur Yvette, France. Mass spectra were obtained on a Ribermag R10 10 by chemical ionisation with NH_3 as reactant gas. Thin layer chromatography were carried out on aluminium slides precoated with silica gel (Merck Kieselgel 60 F254) and preparative chromatography on columns of silica gel (Merck Kieselgel 60, 230-400 mesh ASTM). The ee given for compounds **4a,c,d** are determined by chiral GC analysis of saturated derivatives **24a,c,d** (XE-60-S-val-(S)-α-pea column, L=50m, carrier gas : 2bars He, temperature : injection 240°C, detection 260°C, column 115°C (compounds **24a,c**), 150°C (compound **24d**)). They were confirmed by co-injections of standards. These authentic samples are : (2*S*) and (2*RS*)-**24a** for **4a**; (2*R*) and (2*RS*)-**24c** for **4c**; (2*RS*)-**24d** for **4d** obtained from commercially available starting materials using standard procedures.

Preparation of the optically active oxazolidines ***6*** *:*

1,1-dimethylethyl (4R)-4-ethynyl-2,2-dimethyl-3-oxazolidine carboxylate ***6a.***

A solution of 1,1-dimethylethyl *(4S)*-4-formyl-2,2-dimethyl-3-oxazolidine carboxylate **5**[9] (2.52g, 11mmol) in methanol (60mL) and dimethyl 1-diazo-2-oxopropyl phosphonate **9**[15b] (3.15 g, 16.5 mmol, 1.5 eq.) was placed under an argon atmosphere and cooled to 0°C. K_2CO_3 (3.02g, 22mmol, 2 eq.) was added in one portion. The reaction mixture was stirred for 1h at 0°C and was allowed to warm up to room temperature. After 12h, it was quenched by addition of saturated aqueous NH_4Cl (40mL). The solution was filtered and methanol was evaporated under vacuum. Ethyl acetate (50mL) was poured into the aqueous residue diluted with water (20mL) and the aqueous phase was extracted with ethyl acetate (3x50mL). The combined organic layers were washed with water (50mL), dried over magnesium sulfate, concentrated under reduced pressure and purified by flash silica gel chromatography (cyclohexane / ethyl acetate, 9 / 1) to yield **6a** (1.97g, 80%) as an oil.

$[\alpha]_D^{20}$ -96,5 (c 1.23) {litt[10c] : $[\alpha]_D^{20}$ -73,5 (c 1.01, $CHCl_3$)}. ^1H NMR : 1.50 (s, 12H, 4 CCH_3), 1.65 (s, 3H, CCH_3), 2.29 (br, 1H, C≡CH), 4-4.06 (m, 2H, CH_2O), 4.45-4.65 (m, 1H, CHN). ^{13}C NMR : 24.2, 25.0, 25.7, 26.7, 28.2 ($C\underline{C}H_3$), 48.2 (CHN), 68.5 (CH_2O), 70.1 (C≡$\underline{C}$H), 80.2, 82.6 ($\underline{C}$≡CH, $\underline{C}(CH_3)_3$), 94.2 ($\underline{C}(CH_3)_2$), 151.3 (NCO_2). IR (neat) : 1700 (ν $_{CO}$), 2100 (ν $_{C\equiv C}$), 3300 (ν $_{C\equiv CH}$). MS : 243 $(M+NH_4)^+$, 226 $(M+H)^+$, 187 $(M-CH_2C(CH_3)_2+NH_4)^+$, 170 $(M-CH_2C(CH_3)_2+H)^+$. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.23. Found : C, 63.60; H, 8.09; N, 5.75.

1,1-dimethylethyl (4R)-4-[(2-trimethylsilyl)-ethynyl]-2,2-dimethyl-3-oxazolidine carboxylate ***6b*** **(Table I**, entry 1).

Under an argon atmosphere, 1,1-dimethylethyl *(4R)*-4-ethynyl-2,2-dimethyl-3-oxazolidine carboxylate **6a** (1.1g, 4.9mmol) in anhydrous tetrahydrofuran (25mL) was cooled to -78°C in a

flame-dried flask. *n*-Butyllithium in hexane (3mL, 5.4mmol, 1.1 eq., 2M) and then trimethylsilyl chloride (0.81mL, 5.9mmol, 1.2 eq.) were added dropwise. The reaction mixture was allowed to warm up to 25°C and stirred overnight. Quenching was performed by the addition of cooled water (30mL). The aqueous phase was extracted with ethyl acetate (3x10mL). The combined organic layers were dried over magnesium sulfate, concentrated under vacuum and flash chromatographied on silica gel (cyclohexane / ethyl acetate, 95 / 5) to yield **6b** (870mg, 60%) as a yellow solid.

$[\alpha]_D^{20}$ -121 (c 1.11){litt[10c] : $[\alpha]_D^{20}$ -197 (c 0.64, $CHCl_3$)}. mp 48-49°C. ^1H NMR : 0.17 (s, 9H, $Si(CH_3)_3$, 1.51 (s, 12H, 4 CCH_3), 1.65 (s, 3H, CCH_3), 3.97-4.09 (m, 2H, CH_2O), 4.53 (br, 1H, CHN). ^{13}C NMR : -0.25 ($Si(CH_3)_3$), 24.5, 25.7, 28.3 ($C\underline{C}H_3$), 49.0 (CHN), 68.7 (CH_2O), 80.1, 86.4 ($\underline{C}\equiv C$-Si, $\underline{C}(CH_3)_3$), 94.3 ($\underline{C}(CH_3)_2$), 104.4 ($C\equiv\underline{C}$-Si), 151.3 (NCO_2). IR (neat) : 760, 840 (γ_{SiCH_3}), 1250 ($\delta_{sym\ SiCH_3}$), 1700 (ν_{CO}), 2180 ($\nu_{C\equiv C}$). MS : 298 $(M+H)^+$, 242 $(M-CH_2C(CH_3)_2+H)^+$. Anal. Calcd. for $C_{15}H_{27}NO_3Si$: C, 60.56 ; H, 9.15 ; N, 4.71 ; Si, 9.44. Found : C, 60.27 ; H, 8.87 ; N, 4.54 ; Si, 9.10.

1,1-dimethylethyl (4R)-2,2-dimethyl-4-[prop-1-ynyl]-3-oxazolidine carboxylate ***6c*** *and 2-[(1,1-dimethylethoxy)carbonyl methyl amino]-pent-1-en-3-yne* ***11*** (**Table I**, entry 8).

The alkylation of alkyne **6a** was carried out as described above for compound **6b** on 5.64mmol scale, using 3 eq. of methyl iodide. After flash silica gel chromatography (cyclohexane / ethyl acetate, 95 / 5), 970mg (72%) of **6c** were obtained as a light yellow oil. Enamine **11** (*ca.* 10%) was obtained as a by-product.

Oxazolidine **6c**: $[\alpha]_D^{20}$ -119.9 (c 1.56){litt[10c] : $[\alpha]_D^{20}$ -126 (c 0.8, $CHCl_3$)}. ^1H NMR : 1.49 (s, 12H, 4 CCH_3), 1.62 (s, 3H, CCH_3), 1.80 (d, 3H, J=2.0, $C\equiv CCH_3$), 3.90-4.04 (m, 2H, CH_2O), 4.51 (br, 1H, CHN). ^{13}C NMR : 3.4 ($C\equiv C\underline{C}H_3$), 24.4, 25.8, 28.3 ($C(\underline{C}H_3)_3$, $C(\underline{C}H_3)_2$), 48.2, 48.6 (CHN), 68.5, 68.9 (CH_2O), 70.2, 80.0 (br, $\underline{C}\equiv\underline{C}$, $\underline{C}(CH_3)_3$), 93.8, ($\underline{C}(CH_3)_2$), 151.5 (NCO_2). IR (neat): 1700 (ν_{CO}), 2260 ($\nu_{C\equiv C}$). MS : 257 $(M+NH_4)^+$, 240 $(M+H)^+$.

Enamine **11**: ^1H NMR : 1.48 (s, 9H, $C(CH_3)_3$), 1.96 (s, 3H, $C\equiv CCH_3$), 3.06 (s, 3H, NCH_3), 5.22, 5.24 (2s, 2H, $CH_2=C$). ^{13}C NMR : 4.0 ($C\equiv C\underline{C}H_3$), 28.2 ($C(\underline{C}H_3)_3$), 35.5 ($NCH_3$), 80.3, 85.1 ($\underline{C}\equiv\underline{C}$, $\underline{C}(CH_3)_3$), 114.8 ($\underline{C}H_2=C$), 131.0 ($CH_2=\underline{C}$), 154 (NCO_2). MS : 213 $(M+NH_4)^+$, 196 $(M+H)^+$.

When the reaction was carried out on a larger scale (22mmol of **6a**), **6c** was obtained in 85% yield contaminated with 16% of starting material **6a**.

2-[(1,1-dimethylethoxy)carbonyl methyl amino]-but-1-en-3-yne ***10*** (**Table I**, entry 3).

The enamine **10** (*ca.*16% yield) was obtained as described above for compound **6c** using HMPA as solvent.

^{1}H NMR : 1.41 (s, 9H, $C(CH_3)_3$), 2.87 (s, 1H, C≡CH), 3.00 (s, 3H, NCH_3), 5.28 (s, 1H, CH_2=C), 5.32 (s, 1H, CH_2=C). ^{13}C NMR : 28.1 ($C(\underline{C}H_3)_3$), 35.4 (NCH_3), 76.3 (C≡$\underline{C}$H), 80.1, 80.8 ($\underline{C}$≡CH, $\underline{C}(CH_3)_3$), 116.9 ($\underline{C}H_2$=C), 129.7 (CH_2=$\underline{C}$), 153.7 (NCO_2).

1,1-dimethylethyl (4R)-4-[hex-1-ynyl]-2,2-dimethyl-3-oxazolidine carboxylate ***6d*** *and 2-[(1,1-dimethylethoxy)carbonyl butyl amino]-oct-1-en-3-yne* ***12*** (**Table I**, entry 9).

The alkylation of alkyne **6a** was carried out as described above for compound **6c** on 17.7mmol scale. After flash silica gel chromatography (cyclohexane / ethyl acetate, 95 / 5), 3.43g (70%) of **6d** were obtained as an oil. Enamine **12** (<10%) was obtained as a by-product.

Oxazolidine **6d**: $[\alpha]_D^{20}$ -107.6 (c 1.11). ^{1}H NMR : 0.90 (t, 3H, J=7.0, $CH_2C\underline{H}_3$), 1.42-1.49 (s+m, 16H, 4 CCH_3, $(C\underline{H}_2)_2CH_3$), 1.63 (s, 3H, CCH_3), 2.17 (td, 2H, J=6.7, 2.0, C≡CCH_2), 3.91-4.04 (m, 2H, CH_2O), 4.50 (br, 1H, CHN). ^{13}C NMR : 13.4 ($(CH_2)_2\underline{C}H_3$), 18.2, 21,7 ($(\underline{C}H_2)_2CH_3$), 24.4, 25.1, 25.8, 26.8, 28.3 ($C(\underline{C}H_3)_3$, $C(\underline{C}H_3)_2$), 30.6 (C≡$C\underline{C}H_2$), 48.6 (CHN), 69.1 (CH_2O), 78.9, 79.9, 82.3 ($\underline{C}$≡$\underline{C}$, $\underline{C}(CH_3)_3$), 93.9 $\underline{C}(CH_3)_2$), 151.5 (NCO_2). IR (neat): 1700 (ν CO), 2250 (ν C≡C). MS : 299 $(M+NH_4)^+$, 282 $(M+H)^+$, 243 $(M-CH_2C(CH_3)_2+NH_4)^+$, 226 $(M-CH_2C(CH_3)_2+H)^+$. Anal. Calcd. for $C_{16}H_{27}NO_3$: C, 68.29 ; H, 9.67 ; N, 4.98 ; O, 17.06. Found : C, 68.37 ; H, 9.39 ; N, 4.95 ; O, 16.85.

Enamine **12**: ^{1}H NMR : 0.91 (t, 6H, J=7.2, 2 $(CH_2)_2C\underline{H}_3$), 1.2-1.7 (s+m, 17H, $C(CH_3)_3$, 2 $(C\underline{H}_2)_2CH_3$), 2.30 (t, 2H, J=6.8, C≡CCH_2), 3.45 (t, 2H, J=7.6, NCH_2), 5.26 (s, 1H, CH_2=C), 5.30 (s, 1H, CH_2=C). ^{13}C NMR : 13.5, 13.7 (2 $(CH_2)_2\underline{C}H_3$), 18.7, 19.8, 21.8 (2 $(\underline{C}H_2)_2CH_3$), 28.2 ($C(\underline{C}H_3)_3$), 30.4 (C≡$C\underline{C}H_2$), 47.5 (NCH_2), 77.7, 80.0, 89.0 ($\underline{C}$≡$\underline{C}$, $\underline{C}(CH_3)_3$), 116.8 ($\underline{C}H_2$=C), 129.4 (CH_2=$\underline{C}$), 153.9 (NCO_2). MS : 280 $(M+H)^+$, 241 $(M-CH_2C(CH_3)_2+NH_4)^+$, 224 $(M-CH_2C(CH_3)_2+H)^+$.

Preparation of the optically active aminoalkynols ***7*** *:*

(2R)-2-[(1,1-dimethylethoxy)carbonyl amino]-but-3-yn-1-ol ***7a***

1,1-dimethylethyl *(4R)*-4-ethynyl-2,2-dimethyl-3-oxazolidine carboxylate **6a** (1.15g, 5.1mmol) in methanol (3.5mL) was poured into trifluoroacetic acid (33mL) at 0°C and the reaction mixture was stirred for 2h at room temperature and ether (30 mL) added. TFA was then coevaporated with ether under vaccum so that unprotected aminoalcohol **13** never arrived to dryness. The coevaporation process was repeated three times. Dioxan (30mL) was added and ether was evaporated as to obtain a *ca.* 30mL solution of unprotected aminoalcohol. Saturated aqueous $NaHCO_3$ (30mL) was poured into the solution and pH adjusted to 7-8 *via* addition of powdered $NaHCO_3$. Na_2CO_3 (1.09g, 10.2mmol, 2 eq.) and BocOBoc (2.24g, 10.2mmol, 2 eq.) were added successively at 0°C to the reaction mixture. The latter was allowed to stand at 0°C overnight and stirred at 25°C during 8h. The solution was filtered and the aqueous phase was extracted with ethyl acetate (3x100mL). The combined organic layers were washed with water (2x100mL), dried over

magnesium sulfate, concentrated under reduced pressure and the residue purified by flash silica gel chromatography (cyclohexane / ethyl acetate, 1 / 1) to yield **7a** (0.88g, 93%) as a light yellow solid.

$[\alpha]_D^{20}$ -43 (c 1.08){litt[10c] : $[\alpha]_D^{20}$ -32,5 (c 1.2, $CHCl_3$)}. mp 78-79°C. ^1H NMR : 1.46 (s, 9H, $3CH_3$), 2.34 (d, 1H, J=2.4, C≡CH), 2.5 (br t, 1H, J=6.6, OH), 3.73 (dd, 2H, J=4.6, 6.5, CH_2O), 4.53 (b s, 1H, CHN), 5.06 (b s, 1H, NH). ^{13}C NMR : 28.2 (CH_3), 45.1 (CHN), 65.4 (CH_2O), 72.4 (C≡CH), 80.4, 80.7 (C≡CH, $C(CH_3)_3$), 155.2 (NCO_2). IR (KBr) : 1720 (ν_{CO}), 2145 ($\nu_{C\equiv C}$), 3325 ($\nu_{C\equiv CH}$). MS : 203 $(M+NH_4)^+$, 186 $(M+H)^+$, 147 $(M-CH_2C(CH_3)_2+NH_4)^+$. Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36 ; H, 8.16 ; N, 7.56. Found : C, 58.34 ; H, 7.82 ; N, 7.49.

(2R)-2-[(1,1-dimethylethoxy)carbonyl amino]-4-trimethylsilyl-but-3-yn-1-ol ***7b***

The aminoalcohol **7b** was obtained from **6b** as described above for compound **7a** on 9mmol scale. After flash silica gel chromatography (cyclohexane / ethyl acetate, 7.5 / 2.5), 2.2g (96%) of **7b** were obtained as an oil.

$[\alpha]_D^{20}$ -47 (c 0.91). ^1H NMR : 0.18 (s, 9H, $Si(CH_3)_3$), 1.48 (s, 9H, 3 CCH_3), 2,21 (br, 1H, OH), 3.72 (br t, 2H, CH_2O), 4.57 (br, 1H, CHN), 4,96 (br, 1H, NH). ^{13}C NMR : -0.3 ($Si(CH_3)_3$), 28.2 (CCH_3), 46.1 (CHN), 65.6 (CH_2O), 80.2, 89.1 (C≡C-Si, $C(CH_3)_3$), 102.0 (C≡C-Si), 155.3 (NCO_2). IR (neat) : 770, 850 (γ_{SiCH_3}), 1260 ($\delta_{sym\ SiCH_3}$), 1700 (ν_{CO}), 2180 ($\nu_{C\equiv C}$). MS : 258 $(M+H)^+$.

(2R)-2-[(1,1-dimethylethoxy)carbonyl amino]-pent-3-yn-1-ol ***7c***

The aminoalcohol **7c** was obtained from **6c** as described above for compound **7a** on 4mmol scale. After flash silica gel chromatography (cyclohexane / ethyl acetate, 6.5 / 3.5), 540mg (75%) of **7c** were obtained as a solid.

$[\alpha]_D^{20}$ -51 (c 1.1). mp 64-65°C. ^1H NMR : 1.44 (s, 9H, $C(CH_3)_3$), 1.81 (d, 3H, J=2.3, $C\equiv CCH_3$), 2.49 (br, 1H, OH), 3.66 (d, J=4.8, 2H, CH_2O), 4.48 (br, 1H, CHN), 5.0 (br d, 1H, NH). ^{13}C NMR : 3.4 ($C\equiv CCH_3$), 28.2 ($C(CH_3)_3$), 45.5 (CHN), 66.0 (CH_2O), 75.7, 80.1, 80.5, (C≡C, $C(CH_3)_3$), 155.4 (NCO_2). IR (KBr): 1710 (ν_{CO}), 2240 ($\nu_{C\equiv C}$). MS : 416 $(2M+NH_4)^+$, 399 $(2M+H)^+$, 234 $(M+NH_3+NH_4)^+$, 217 $(M+NH_4)^+$, 200 $(M+H)^+$, 161 $(M-CH_2C(CH_3)_2+NH_4)^+$, 144 $(M-CH_2C(CH_3)_2+H)^+$. Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.28 ; H, 8.60 ; N, 7.03 ; O, 24.09. Found : C, 60.52 ; H, 8.47 ; N, 6.93 ; O, 24.19.

(2R)-2-[(1,1-dimethylethoxy)carbonyl amino]-oct-3-yn-1-ol ***7d***

The aminoalcohol **7d** was obtained from **6d** as described above for compound **7a** on 5mmol scale. After flash silica gel chromatography (cyclohexane / ethyl acetate, 7.5 / 2.5), 990mg (87%) of **7d** were obtained as a solid.

$[\alpha]_D^{20}$ -44 (c 0.95). mp 48-49°C. ^{1}H NMR : 0.90 (t, 3H, J=7.2, $(CH_2)_2\underline{C}H_3$), 1.29-1.56 (s+m, 13H, $C(CH_3)_3$, $(\underline{C}H_2)_2CH_3$), 2,18 (td, 2H, J=6.8, 2.1, $C{\equiv}C\underline{C}H_2$), 2.44 (br, 1H, OH), 3.66 (dd, 2H, J=6.4, 4.8, CH_2O), 4.51 (br, 1H, CHN), 4,94 (br, 1H, NH). ^{13}C NMR : 13.5 ($(CH_2)_2\underline{C}H_3$), 18.2, 21,8 ($(\underline{C}H_2)_2CH_3$), 28.2 ($C(\underline{C}H_3)_3$), 30.5 ($C{\equiv}\underline{C}CH_2$), 45.7 (CHN), 66.1 ($CH_2O$), 76.3, 80.1, 85.2, ($\underline{C}{\equiv}\underline{C}$, $\underline{C}(CH_3)_3$), 155.3 (NCO_2). IR (KBr) : 1700 (ν CO), 2250 (ν C≡C). MS : 259 $(M+NH_4)^+$, 242 $(M+H)^+$, 203 $(M-CH_2C(CH_3)_2+NH_4)^+$, 186 $(M-CH_2C(CH_3)_2+H)^+$. Anal. Calcd. for $C_{13}H_{21}NO_3$: C, 64.70 ; H, 9.60 ; N, 5.80 ; O, 19.89. Found : C, 64.64 ; H, 9.28 ; N, 5.68 ; O, 20.07.

(2R)-2-acetamidobut-3-ynyl acetate ***14***

1,1-dimethylethyl *(4R)*-4-ethynyl-2,2-dimethyl-3-oxazolidine carboxylate **6a** (3.44g, 16mmol) in methanol (4.5mL) was poured into trifluoroacetic acid (45mL) at 0°C and the reaction mixture was stirred for 2h at room temperature. TFA was coevaporated with ether (4x30mL) as described above for compound **7a**. Pyridine (30mL) was added and a solution of acetyl chloride (0.58mL, 3 eq.) in chloroform (3.1ml) was added dropwise. After 2h, the reaction mixture was quenched by addition of methanol (*ca.* 1 eq.) and pyridine was coevaporated with toluene to give a solid which was dissolved in ether. The solution was filtered and the filtrate was concentrated under vacuum. The residue was purified by flash silica gel chromatography (methanol / ethyl acetate, 1 / 9) to yield **14** (1.68g, 65%) as a light yellow solid.

$[\alpha]_D^{20}$ -28.6 (c 1.16). mp 76-77°C. ^{1}H NMR : 2.04 (s, 3H, CH_3CO), 2.13 (s, 3H, CH_3CO), 2.33 (d, 1H, J=2.4, C≡CH), 4.17 and 4.28 (2 dd, 2H, J=11.1, 4.7 and J=11.1, 5.8, CH_2O), 5.02-5.14 (m, 1H, CHN), 6.02 (br d, 1H, NH). ^{13}C NMR : 20.6, 22.9 (CH_3), 40.4 (CHN), 65.0 (CH_2O), 72.3 ($C{\equiv}\underline{C}H$), 79.6 ($\underline{C}{\equiv}CH$), 169.4, 170.6 ($CH_3\underline{C}O$). IR (nujol) : 1670, 1740 (ν CO), 3270 (ν C≡CH). Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.79 ; H, 6.55 ; N, 8.28 ; O, 28.37. Found : C, 56.72 ; H, 6.57 ; N, 7.99 ; O, 28.30.

(2R)-2-acetamidobut-3-yn-1-ol ***7e***

A solution of *(2R)*-2-acetamidobut-3-ynyl acetate **14** (1.57g, 12mmol) in methanol (20mL) was cooled to 0°C. Sodium methoxide (100mg, 2mmol) was added to the solution. After 3h at 0°C, the reaction mixture was quenched *via* acidification by addition of Amberlite IRA93 H^+ resin in order to obtain pH=7. The solution was then filtered and the resin washed with methanol. The filtrate was concentrated under reduced pressure and the residue purified by flash silica gel chromatography (ethyl acetate / methanol, 95 / 5) to yield **7e** (1.04g, 88%) as a white solid.

$[\alpha]_D^{20}$ -75.6 (c 1.0, CH_3OH). mp 122-123°C. ^1H NMR (200 MHz, DMSO-*d6*) : 1.82 (s, 3H, CH_3CO), 3.14 (d, 1H, J=2.4, C≡CH), 3.42 (t, 2H, J=6.2, CH_2O), 4.52 (m, 1H, CHN), 5.07 (t, 1H, J=6.0, OH), 8.23 (br d, 1H, J=8.3, NH). ^{13}C NMR (50.3 MHz, DMSO-*d6*) : 22.5 (CH_3), 42.9 (CHN), 63.3 (CH_2O), 73.6 (C≡CH), 82.7 (C≡CH), 169.7 (CH_3CO). MS : 145 $(M+NH_4)^+$, 128 $(M+H)^+$.

*Preparation of the optically active N-protected β,γ-alkynylglycine derivatives **4** :*

*(2R)-2-[(1,1-dimethylethoxy)carbonyl amino]-but-3-ynoic acid **4a** (N-Boc-D-ethynyl glycine) and N-propynoyl-1,1-dimethylethyl carbamate **17a***

Concentrated H_2SO_4 (0.85mL) was added to a solution of CrO_3 (970mg, 9mmol, 3 eq.) in water (2.9mL) and cooled to 0°C. A solution of *(2R)*-2-[(1,1-dimethylethoxy)carbonyl amino]-but-3-yn-1-ol **7a** (580mg, 3mmol) in acetone (30mL) was added dropwise to the Jones reagent over 1h40min. The reaction mixture was stirred at 0°C during 2h and allowed to warm up and to stand at room temperature overnight. Isopropanol was added until decoloration of the solution (3-4 drops) and the latter was filtered. The filtrate was evaporated to dryness and the residue was dissolved in ethyl acetate (40mL). The resulting solution was washed three times with saturated $NaHCO_3$ (20mL) and the aqueous layer pH adjusted to 2-3 with $KHSO_4$ as soon as separated. The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum to give the imide **17a** (160mg, 22%) as an oil. The combined acidic aqueous solutions were extracted with ethyl acetate (3x40mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure to give N-Boc-D-ethynyl glycine **4a** (200mg, 32%) as an oil. Purification by preparative HPLC performed at this stage using Delta pak column Waters C18, 100Å, 15µ, flow rate : 20ml/min., eluent : water / acetonitrile = 85/15 showed no significant improvement in purity (NMR, optical rotation).

Acid **4a** : $[\alpha]_D^{20}$ -53.9 (c 0.89). ee= 93%. ^1H NMR : 1.46 (s, 9H, $3CH_3$), 2.42 (d, 1H, J=2.5, C≡CH), 4.91 (br s, 0.4H, CHN), 5.14 (br d, 0.6H, J~6, CHN), 5.39 (br d, 0.6H, J~6, NH), 7.09 (br s, 0.4H, NH), 9.65 (m, 1H, COOH). ^{13}C NMR : 28.1 (CH_3), 45.4, 46.2 (CHN), 72.0, 72.9 (C≡CH), 81.2, 82.7 (C≡CH, $C(CH_3)_3$), 155.0, 156.0 (NCO_2), 170.0, 170.9 (COOH). IR (neat) : 1710 (ν_{CO}), 2120 ($\nu_{C\equiv C}$), 3300 ($\nu_{C\equiv CH}$). MS : 217 $(M+NH_4)^+$, 200 $(M+H)^+$, 161 $(M-CH_2C(CH_3)_2+NH_4)^+$.

Imide **17a**: ^1H NMR : 1.52 (s, 9H, $3CH_3$), 3.29 (s, 1H, C≡CH), 7.86 (br s, 1H, NH). ^{13}C NMR : 27.8 (CH_3), 75.6 (C≡CH), 80.2, 83.7 (C≡CH, $C(CH_3)_3$), 148.9, 150.8 (NCO_2, CON). MS : 187 $(M+NH_4)^+$.

(2R)-2-[(1,1-dimethylethoxy)carbonyl amino]-4-trimethylsilyl-but-3-ynoic acid ***4b*** *and N-(3-trimethylsilylpropynoyl)-1,1-dimethylethyl carbamate* ***17b***

The N-Boc aminoacid **4b** and the imide **17b** were obtained as described above for compounds **4a** and **17a** on 2.16g (8.4mmol) scale.

Acid **4b**: oil. Yield 33%. $[\alpha]_D^{20}$ -60.8 (c 1.15). ^1H NMR : 0.18 (s, 9H, $Si(CH_3)_3$, 1.46 (s, 9H, $C(CH_3)_3$), 4.90 (br, 0.4H, CHN), 5.10 (br d, 0.6H, J~7.5, CHN), 5.26 (br d, 0.6H, J~7.5, NH), 7.23 (br s, 0.4H, NH), 9.60 (br, 1H, COOH). ^{13}C NMR : -0.5 ($Si(CH_3)_3$), 28.1 ($C(\underline{C}H_3)_3$), 46.2 (CHN), 80.8, 95.7, 97.7 ($\underline{C}\equiv\underline{C}$, $\underline{C}(CH_3)_3$), 154.8 (NCO_2), 171.4 (COOH). IR (NaCl) : 760, 850 (γ $_{SiCH_3}$), 1260 (δ_{sym} $_{SiCH_3}$), 1700 (ν $_{CO}$), 2180 (ν $_{C\equiv C}$). MS : 289 $(M+NH_4)^+$; 272 $(M+H)^+$; 233 $((M-CH_2C(CH_3)_2)+NH_4)^+$.

Imide **17b**: oil. Yield 23%. ^1H NMR : 0.26 (s, 9H, $Si(CH_3)_3$), 1.52 (s, 9H, $C(CH_3)_3$), 7.50 (br s, 1H, NH). ^{13}C NMR : -1.0 ($Si(CH_3)_3$), 27.8 ($C(\underline{C}H_3)_3$), 83.2, 95.8, 98.0 ($\underline{C}\equiv\underline{C}$, $\underline{C}(CH_3)_3$), 148.5, 150.5 (NCO_2, CON). MS : 259 $(M+NH_4)^+$; 203 $((M-CH_2C(CH_3)_2)+NH_4)^+$.

(2R)-2-[(1,1-dimethylethoxy)carbonyl amino]-pent-3-ynoic acid ***4c*** *and N-(2-butynoyl)-1,1-dimethylethyl carbamate* ***17c***

The N-Boc aminoacid **4c** and the imide **17c** were obtained as described above for compounds **4a** and **17a** on 1.05g (5.3mmol) scale.

Acid **4c**: oil. Yield 26%. $[\alpha]_D^{20}$ -46 (c 1.1). ee= 91%. ^1H NMR : 1.43 (s, 9H, $C(CH_3)_3$), 1.82 (d, 3H, J=2.5, $C\equiv CCH_3$), 4.84 (br, 0.3H, CHN), 5.04 (br, 0.7H, CHN), 5.34 (br, 0.7H, NH), 6.43 (br, 0.3H, NH), 8.86 (br, 1H, COOH). ^{13}C NMR : 3.5 ($C\equiv C\underline{C}H_3$), 28.1 ($C(\underline{C}H_3)_3$), 45.7 (CHN), 72.1, 81.2, 87.3, ($\underline{C}\equiv\underline{C}$, $\underline{C}(CH_3)_3$), 157.0 (NCO_2), 172.2 (COOH). IR (neat) : 1720 (ν $_{CO}$), 2230 (ν $_{C\equiv C}$). MS : 231 $(M+NH_4)^+$; 214 $(M+H)^+$.

Imide **17c**: oil. Yield 24%. ^1H NMR : 1.53 (s, 9H, $C(CH_3)_3$), 2.07 (s, 3H, $C\equiv CCH_3$), 7.69 (br, 1H, NH). ^{13}C NMR : 4.2 ($C\equiv C\underline{C}H_3$), 27.8 ($C(\underline{C}H_3)_3$), 74.0, 80.0, 83.0, ($\underline{C}\equiv\underline{C}$, $\underline{C}(CH_3)_3$), 146, 149.1 (NCO_2, CON).

(2R)-2-[(1,1-dimethylethoxy)carbonyl amino]-oct-3-ynoic acid ***4d*** *and N-(2-heptynoyl)-1,1-dimethylethyl carbamate* ***17d***

The N-Boc aminoacid **4d** and the imide **17d** were obtained as described above for compounds **4a** and **17a** on 1.03g (4.3mmol) scale.

Acid **4d**: oil. Yield 37%. $[\alpha]_D^{20}$ -8.0 (c 1.01). ee= 91%. ^1H NMR : 0.87 (t, 3H, J=7.0, $(CH_2)_2C\underline{H}_3$), 1.42 (s+m, 13H, $C(CH_3)_3$, $(C\underline{H}_2)_2CH_3$), 2,16 (td, 2H, J=6.8, 2.2, $C\equiv CCH_2$), 4.82 (br s, 0.3H, CHN), 5.02 (br d, 0.7H, J~6.8, CHN), 5,34 (br d, 0.7H, 7.6, NH), 6,79 (br s, 0.3H, NH), 10.33 (br, 1H, COOH). ^{13}C NMR : 13.4 ($(CH_2)_2\underline{C}H_3$), 18.2, 21.7 ($(\underline{C}H_2)_2CH_3$),

28.1 ($C(\underline{C}H_3)_3$), 30.2 ($C\equiv C\underline{C}H_2$), 45.7 (CHN), 73.2, 80.6, 85.3, ($\underline{C}\equiv\underline{C}$, $\underline{C}(CH_3)_3$), 154.9 (NCO_2), 172.1 (COOH). IR (neat) : 1720 (ν_{CO}), 2240 ($\nu_{C\equiv C}$). MS : 273 $(M+NH_4)^+$, 256 $(M+H)^+$, 217 $((M-CH_2C(CH_3)_2)+NH_4)^+$, 200 $((M-CH_2C(CH_3)_2)+H)^+$.

Imide **17d**: oil. Yield 11%. ^1H NMR : 0.93 (t, 3H, J=7.2, $(CH_2)_2\underline{C}H_3$), 1.35-1.65 (s+m, 13H, $C(CH_3)_3$, $(\underline{C}H_2)_2CH_3$), 2,40 (t, 2H, J=7.0, $C\equiv CCH_2$), 7.64 (br, 1H, NH). ^{13}C NMR : 13.3 ($(CH_2)_2\underline{C}H_3$), 18.5, 21.8 ($(\underline{C}H_2)_2CH_3$), 27.8 ($C(\underline{C}H_3)_3$) , 29.3 ($C\equiv C\underline{C}H_2$), 74.4, 82.8, 94.8, ($\underline{C}\equiv\underline{C}$, $\underline{C}(CH_3)_3$), 148.9, 151.6 (NCO_2, CON). MS : 243 $(M+NH_4)^+$; 226 $(M+H)^+$; 187 $((M-CH_2C(CH_3)_2)+NH_4)^+$.

*(2R)-2-acetamido-but-3-ynoic acid **4e** and N-acetyl propynamide **17e***

The N-Ac aminoacid **4e** and the imide **17e** were obtained as described above for compounds **4a** and **17a** on 200mg (1.6mmol) scale, except that they could not be separated. The crude residue (acid **4e**/ imide **17e** = 1 / 2) was obtained as a yellow oil (60mg). Unique obtention of imide **17e** is observed when 10 eq.of Jones reagent is used.

Acid **4e**: ^1H NMR (200 MHz, DMSO-*d6*) : 1.97 (s, 3H, CH_3CO), 3.34 (d, 1H, J=2.7, C≡CH), 5.05 (dd, 1H, J=2.7, 7.7, CHN), 8.74 (d, 1H, J=7.7, NH), 11.31 (br, 1H, COOH). ^{13}C NMR (50.3 MHz, DMSO-*d6*) (δ) : 23.3 (CH_3), 44.6 (CHN), 75.6 ($C\equiv\underline{C}H$), 83.7 ($\underline{C}\equiv CH$), 171.1, 171.2 ($CH_3\underline{C}O$, COOH).

Imide **17e** : ^1H NMR (200 MHz, $CDCl_3$) : 2.46 (s, 3H, CH_3CO), 3.15 (s, 1H, C≡CH), 8.38 (br, 1H, NH). ^{13}C NMR (50.3 MHz, DMSO-*d6*) (δ) : 25.2 (CH_3), 77.5 ($C\equiv\underline{C}H$), 81.6 ($\underline{C}\equiv CH$), 151.2 (CON), 170.5 ($\underline{C}OCH_3$). MS : 129 $(M+NH_4)^+$, 112 $(M+H)^+$.

*(2R)-N-Boc-aminobutyric acid **25a** and N-propanoyl-1,1-dimethylethyl carbamate **26** from crude **4a***

The crude *(2R)*-2-[(1,1-dimethylethoxy)carbonyl amino]-but-3-ynoic acid **4a** containing imide **17a** (2.33g, 11.7mmol) was dissolved in methanol (135mL). A suspension of palladium (5%) on charcoal (585mg) in methanol was added to the solution and the reaction mixture was placed under a saturated hydrogen atmosphere. After 3h, the solution was filtered on celite and concentrated under vacuum. The residue was dissolved in ethyl acetate (100mL). The organic layer was washed with saturated $NaHCO_3$ (3x50mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the imide **26**[47] as a white solid (730mg, 28% yield based on alcohol **7a**). The combined aqueous phases were acidified with $KHSO_4$ to pH=2-3 and extracted with ethyl acetate (3x100mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated to dryness under vacuum to yield N-Boc-D-aminobutyric acid **25a** (1.04g, 33% yield based on alcohol **7a**) as an oil.

Acid **25a**: $[\alpha]_D^{20}$ +4.75 (c 2.52, CH_2Cl_2) (litt[49] $[\alpha]_D^{20}$ +9.5°, c 2.2, CH_2Cl_2). ^1H NMR : 1.00 (t, 3H, J=7.4, $CH_2\underline{CH_3}$), 1.47 (s, 9H, $C(CH_3)_3$), 1.65-1.98 (m, 2H, CH_2), 4.15 (br s, 0.3H, CHN), 4.30 (br m, 0.7H, CHN), 5.10 (br d, 0.7H, J=7.9, NH), 6.50 (br s, 0.3H, NH), 10.15 (br, 1H, COOH). MS : 221 $(M+NH_4)^+$, 204 $(M+H)^+$.

Imide **26**: mp 105-106°C (litt[47] mp 120-121°C). ^1H NMR : 1.15 (t, 3H, J=7.3, $CH_2\underline{CH_3}$), 1.49 (s, 9H, $C(CH_3)_3$), 2.75 (q, 2H, J=7.3, CH_2), 7.47 (m, 1H, NH). MS : 191 $(M+NH_4)^+$, 174 $(M+H)^+$.

Methyl (2R) 2-[(1,1-dimethylethoxy)carbonyl amino] butyrate ***24a***[46a]

A solution of *(2R)*-N-Boc-aminobutyric acid **25a** obtained as described above (200mg, 1mmol) and triphenylphosphine (288mg, 1.1mmol, 1.1 eq.) in ether (2mL) was heated under reflux. Methanol (48μL, 1.2mmol, 1.2 eq.) and diethyl azodicarboxylate (174μL, 1.2mmol, 1.2 eq.) were successively added dropwise to the hot reaction mixture. The latter was allowed to stand at room temperature for 1h and then overnight at 0°C. The precipitate formed was eliminated by filtration, the filtrate concentrated under reduced pressure and the residue purified by silica gel chromatography (ethyl acetate / cyclohexane, 1.5 / 8.5) to yield **24a** (160mg, 75%) as a yellow oil.

$[\alpha]_D^{20}$ +31.7 (c 2.3, MeOH){L-isomer : litt.[46a]: $[\alpha]_D^{20}$ -39 (c=2, MeOH), from commercially available aminobutyric acid : $[\alpha]_D^{20}$ -33 (c=2.3, MeOH)}. ee=93% by chiral GC analysis (see *General Methods*). ^1H NMR : 0.93 (t, 3H, J=7.4, $CH_2\underline{CH_3}$), 1.45 (s, 9H, $C(CH_3)_3$), 1.60-1.95 (m, 2H, CH_2), 3.74 (s, 3H, $COOCH_3$), 4.26 (m, 1H, CHN), 5.05 (m,1H, NH).

Methyl esters **24c,d** used for the determination of ee were synthesized from isolated **4c,d** as described above for **24a**. Spectral data were consistent with the assigned structures, literature data and/or authentic samples.

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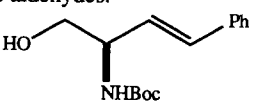

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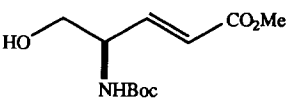

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