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# Ethynylglycine synthon from Garner's aldehyde: a useful precursor for the synthesis of non-natural amino acids

## Minireview Article

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**Summary.** The ethynylglycine synthon, namely (*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyl-oxazolidine, can be obtained through the synthetic elaboration of naturally occurring serine. This compound has been exploited as a helpful and versatile non-racemic building block to be used for the design and synthesis of biologically important compounds, mainly non-natural  $\alpha$ -amino acids. Taking advantage of the terminal acetylene moiety several synthetic applications can be designed. Metalation followed by trapping with electrophiles or Cu/Pd catalysed coupling with aromatic halogenides are shown to deliver useful precursors of ethynylglycine derivatives. Additions of bimetallic reagents like stannyl- or silylcuprates are useful entries for the regio- and stereoselective functionalization of the lateral chain, aimed at the synthesis of modified vinylglycine precursors.

An overview of our recent work in the field will be given, and the use of ethynylglycine synthon in the synthesis of non-racemic saturated and unsaturated non-natural amino acids will be briefly reviewed.

**Keywords:** Amino acids – Synthesis – Precursors – Organometallics – Ethynylglycine

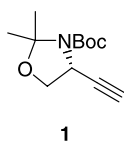
Amino acids have some fundamental biological roles: for instance, they are used as enzyme inhibitors or, more in general, investigated as therapeutic agents, in addition they are important for probing the structural requirements for the bioactivity of numerous peptides and proteins (Barrett, 1985; Andrews and Tabor, 1999). For these reasons, large efforts have been made in recent years to the preparation of homochiral non-natural amino acids (Duthaler, 1994; Ohfuné, 1992; Sardina and Rapoport, 1996; Williams, 1989). Several methods have been developed to introduce chirality during the synthesis of a new amino acid. In many cases the requested configuration is provided by the starting material and maintained throughout the synthetic sequence

by means of reactions that do not affect the stereocenter. Naturally occurring chiral compounds are often used for this purpose (Coppola and Shuster, 1987), but the synthesis of new useful non-racemic building blocks has also received a large attention.

Research in our laboratories has recently focused on the synthesis of unusual amino acids (Reginato et al., 1997, 1998, 1999; Meffre et al., 1999, 2001; Meffre, 1999; Meffre and Durand, 2002; Dave et al., 2003) and in the course of our studies we reported the first synthesis of ethynyloxazolidine **1** (Fig. 1).

Due to the simultaneous presence of the oxazolidine moiety, that is widely used as synthetic equivalent of  $\alpha$ -amino acids, and of the unsaturated lateral chain, that consents to several synthetic elaborations, this compound can be considered as a very useful building block for the synthesis of this class of compounds.

Oxazolidine **1** can be easily prepared from Garner's aldehyde **2** (Fehrentz and Castro, 1983; Garner and Park, 1987; Meffre et al., 1994; Dondoni and Perrone, 1997) either by a two steps sequence (Reginato et al., 1995; Cameron and Khambay, 1998; Falorni et al., 1998) *via* dibromovinyl intermediate (Corey-Fuchs strategy) (Corey and Fuchs, 1972) or *via* direct aldehyde-to-alkyne one-carbon homologation, using dimethyl 1-diazo-2-oxopropylphosphonate (Ohira reagent) (Ohira, 1989). This phosphonate must be first prepared by reaction of the commercially available dimethyl 2-oxopropyl phosphonate **3** and the potentially explosive tosyl azide (TsN<sub>3</sub>). Very

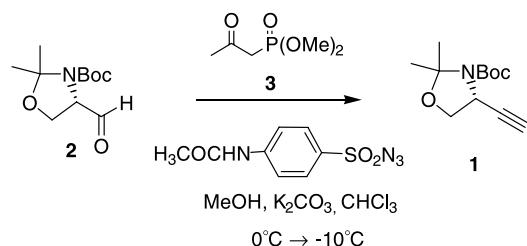


**Fig. 1.** 2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine

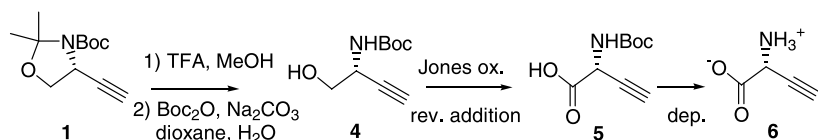
recently, we have improved this procedure and shown that Garner's aldehyde can be directly transformed into compound **1** using a simple one-pot multicomponent process. This involves the *in situ* formation of dimethyl 1-diazo-2-oxopropyl phosphonate from **3** and the more friendly 4-acetamidobenzene sulfonyl azide (Meffre et al., 2002) (Scheme 1).

Starting with D- or L-serine, compound **1** has been obtained in both configurations and its optical purity confirmed >95% by <sup>1</sup>H-NMR analysis of the diastereomeric Mosher's esters prepared from the amino alcohol obtained after deprotection.

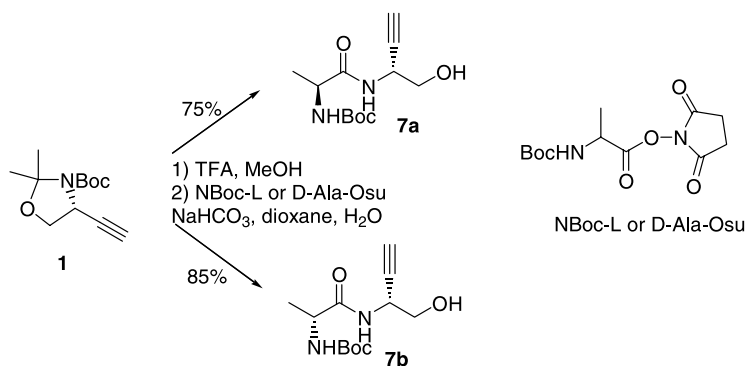
Compound **1** has been used as starting material for the first stereoselective synthesis (Meffre et al., 1995 and 1996) of  $\alpha$ -ethynylglycine **6** as shown in Scheme 2. This unsaturated amino acid, which can be obtained from cul-



**Scheme 1**



**Scheme 2**

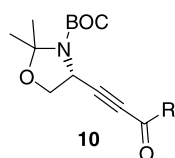
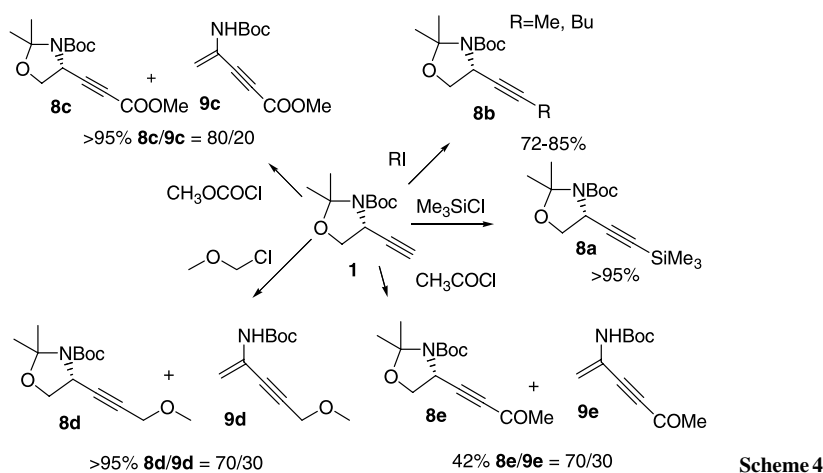


**Scheme 3**

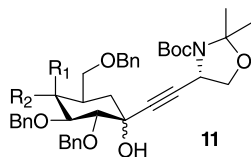
tures of *Streptomyces Catenulae*, (Kuroda et al., 1980) displays antimicrobial activity against gram-positive bacteria and interacts with D-cycloserine.

While amino acid **6** is extremely unstable, oxazolidine **1**, as its direct precursor, can be conveniently used to prepare stable dipeptide precursors like **7a, b** (Scheme 3) or in the synthesis of optically active ethynylglycine derivatives (Meffre and Le Goffic, 1996). Different functional groups on the terminal position of the lateral chain could be easily introduced, for instance, through metalation and reaction with electrophiles (Corriu et al., 1984). This approach leads to the synthesis of a series of previously unknown compounds **8a–e**, as shown in Scheme 4 (Reginato et al., 1995 and 1997; Meffre et al., 1996). Clean silylation and alkylation to **8a** and **8b** were realized using chlorotrimethylsilane, iodomethane, and iodobutane as electrophiles. Reaction with methyl chloroformate and methoxymethyl-chloride gave also good yields, but in these cases, together with **8c** and **8d**, variable amounts of by-products **9c**, and **9d** were obtained. Unfortunately compound **8e**, was formed only in low yields hampering a further generalisation of the method. More recently, condensation with aldehydes has been described (Serrat et al., 1999) which provides, after oxidation, acetylenic ketones of structure **10** (Fig. 2). These compounds have been used in the stereoselective synthesis of novel quinolyl glycines, (Cabarrocas et al., 2000a) enantiomerically pure pyrazolyl- $\beta$ -amino alcohols (Cabarrocas et al., 2000b) and quinolyl- $\beta$ -amino alcohols (Cabarrocas et al., 2001).

Metalated oxazolidine **1** was also employed in the ethynylation of sugar lactones. A mixture of diastereomeric galactose oxazolidinyl acetylenes **11** (Fig. 3) was formed



**Fig. 2.** Useful precursors of enantiomerically pure quinolyl and pyrazolyl  $\beta$ -amino alcohols and glycines



**Fig. 3.** Ethynylated sugar lactones

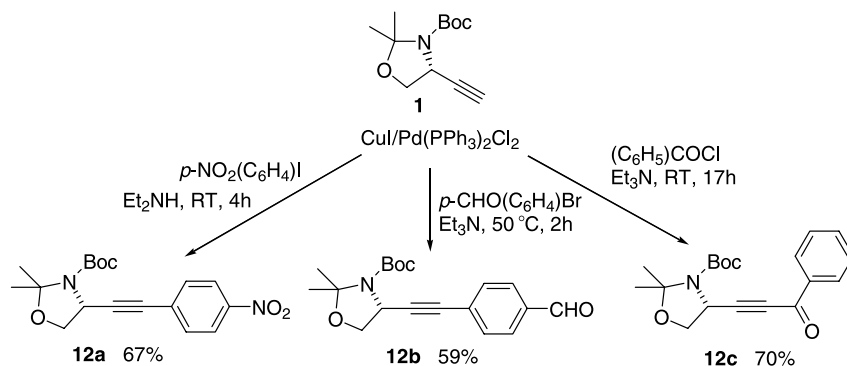
and used as intermediates for the synthesis of  $\beta$ -D-linked methylene isomers of glycosyl serines (Dondoni et al., 2001).

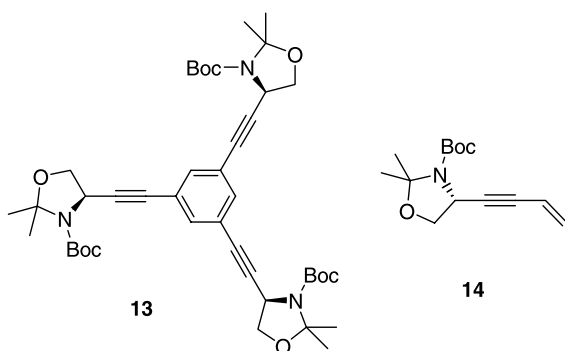
In order to circumvent the problems connected with the formation of by-products, we considered a second, milder approach. Sonogashira coupling between terminal alkynes and aromatic halides in the presence of a copper–palladium

catalyst is a well known, efficient, high yielding and chemoselective (Sonogashira et al., 1975) procedure which has been frequently used for introducing differently substituted aromatic rings. This simple approach was applied successfully to prepare compounds **12a–c** (Reginato et al., 1997) as shown in Scheme 5.

The same strategy was used later by other groups. Compound **1** has been coupled with a variety of aromatic and vinylic halides and triflates under Pd catalysis to form a series of aryl-alkynes amino acids precursors like **13** (Crisp et al., 1997), or an ene-yne aminoacid precursor like **14** (Cameron and Cambay, 1998) (Fig. 4).

We further demonstrated the synthetic versatility of compound **1** in the synthesis of vinylglycine precursors, a class of compounds which has received special attention for their biological interest. Addition of metal hydride or dimetallic reagents across the triple bond is known as an easy and practical way for obtaining substituted double bonds. We started to exploit the addition of mixed tributylstannylcuprate **15** (Lipshutz et al., 1989) on to compound **1**, as it can provide an efficient entry to  $\beta,\gamma$ -substituted vinyl glycine precursor with a defined *E* geometry of the double bond (see Scheme 6).





**Fig. 4.** Aryl-alkynes and ene-yne amino acids precursors

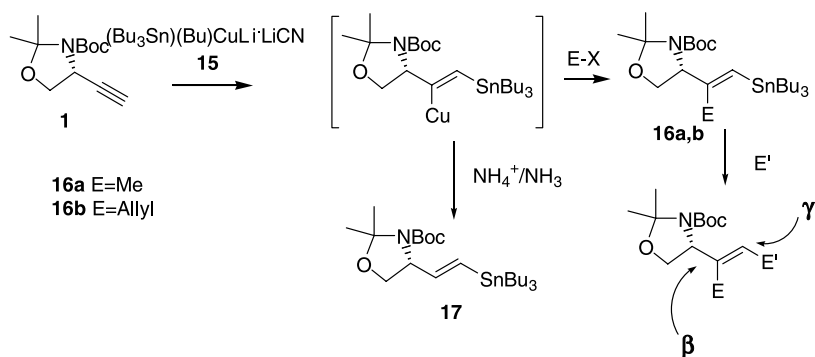
Addition, when followed by hydrolytic work-up, gave  $\gamma$ -stannylated (*E*)-ethenyloxazolidine **17** as a single reaction product in very high yield (Reginato et al., 1997). Trapping of the vinyl copper intermediate with allylbromide or MeI gave the corresponding  $\beta$ -functionalized vinylstannanes

**16a, b**. Finally a new series of  $\gamma$ -substituted (*E*)-ethenyloxazolidine **18a–e** resulted from Pd-catalysed Stille coupling (Stille, 1986) of **17** with several electrophiles (Scheme 7) (Reginato et al., 1997).

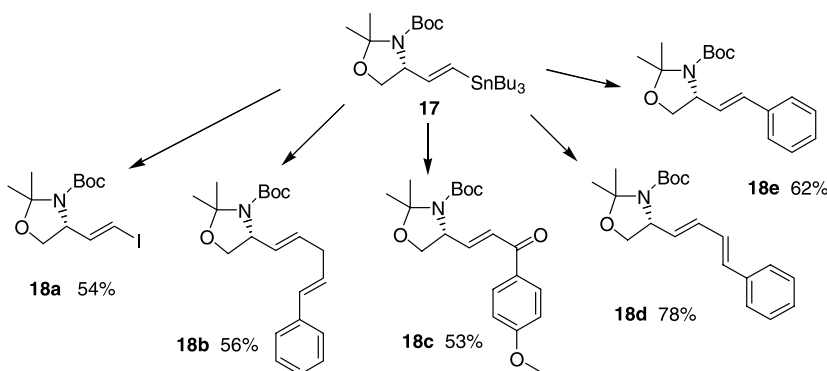
The same approach was used by Crisp (Crisp et al., 1997) too. In this case the stannylated precursor was prepared through a less selective AIBN initiated hydrostannylation and both *E* and *Z* isomers were obtained in 85/15 ratio.

Non-racemic amino ketones were also obtained via a high yielding two step Pd catalyzed allylation/Wacker oxidation (Reginato et al., 2000). Compound **19** is a useful intermediate for obtaining 2,6 disubstituted piperidines (Scheme 8).

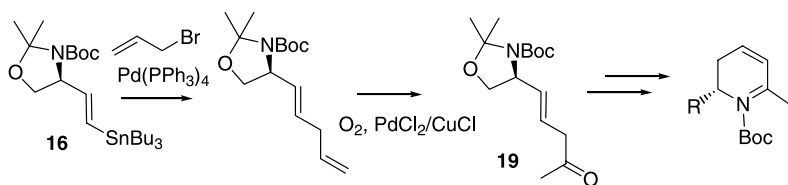
A similar approach was used also in the synthesis of a new class of silicon containing amino acids. Silicon is an essential element for many biological systems, (Tacke, 1999) and trialkylsilyl chains are known to have hydrophobic properties which might be relevant for biological activity (Tacke, 1985; Tacke and Linoh, 1989) e.g. in the



**Scheme 6**



**Scheme 7**



**Scheme 8**

field of lipophilic amino acids. Silylated amino acids can also be responsible of enhancing biological activity and proteolytic stability of peptides, as it has already been observed in the search for stable rennin inhibitors (Weidman, 1992). Moreover, because of the high reactivity reported for organosilanes (Fleming et al., 1997), silylated amino acids can be considered as useful optically active starting materials for a variety of synthetic applications.

Addition of trimethylsilylcyanocuprates **20a–c** to compound **1** and hydrolytic workup gave the corresponding  $\gamma$ -silylated (E)-ethenyloxazolidine **21a–c** (Reginato et al., 1997 and 1999) (Scheme 9), an useful precursor of silicon containing amino acids.

Phenyldimethylsilylcyanocuprate **20b** was selected for introducing a dimethylphenylsilyl group which has the advantage of being converted, if necessary, into a hydroxyl group (Fleming et al., 1995). This transformation can find several applications. A recently reported copper-catalyzed procedure was applied (Lipshutz et al., 1998) in this case, which minimized the amount of silyl ligand involved and requires only a small percentages of CuCN, thus making it particular appealing for large scale reactions. Vinylsilane **21b** was obtained, using this procedure, in multigram quantities.

Vinylsilanes **21a–c**, after reduction of the double bond, hydrolytic removal of the acetone protecting group and oxidation, afforded a new class of silylated amino acids **22a–c** (Scheme 10). The oxidative step was the most chal-

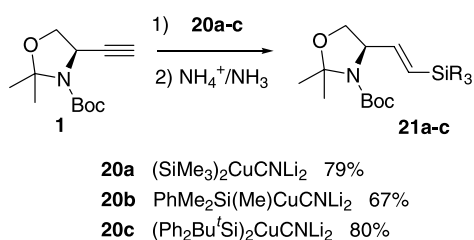
lenging and the best result was obtained using periodic acid ( $\text{H}_5\text{IO}_6$ ) in the presence of a catalytic amount of chromic anhydride (Zhao et al., 1998).

Remarkably, using this method, unsaturated amino alcohols **23** could also be efficiently oxidized to afford unsaturated amino acid **24** in satisfactory yield (Reginato et al., 1999) (Scheme 11). The efficiency of the oxidative step in the latter case is in agreement with previous findings that unsaturated amino acids are stabilized by electron donor substituents on the terminal double bond (Beaulieu et al., 1991). The trialkylsilyl groups are thus suitable substituents for stabilizing vinylglycine derivatives. For characterization purposes, crude amino acids were transformed into the corresponding methyl esters and isolated in pure form.

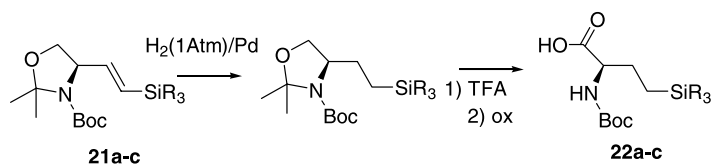
Silylated amino acids were capable of undergoing typical reactions associated with peptide synthesis. For instance **22a, b** were coupled with (L)-leucine methyl ester using the diethylcyanophosphonate/diisopropylethylamine (DEPC/DIEA) method to produce dipeptides **25a, b**. Under similar conditions disilylated dipeptide **26** was also obtained in good yield (Fig. 5).

Ethynyloxazolidine **1** has been also used in the addition of diisopinocampheyl-borane ( $\text{Ipc}_2\text{BH}$ ) followed by transesterification with benzpinacol to obtain the alkenylboronic ester **27** (Pietruszka et al., 2003) (Scheme 12), which, although obtained in low yield, has been shown as a promising intermediate for new cyclopropane containing amino acids.

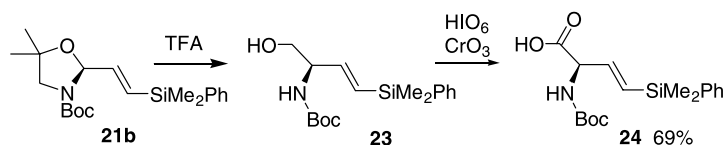
Finally, ethynyloxazolidine **1** has been reacted with nitrile oxide to afford isoxazole **28** that has been transformed into amino acid **29** (Falorni et al., 1998) (Scheme 13). Very recently the same cycloaddition has been carried out by generating nitrile oxides *in situ* from nitroalkanes, under microwaves irradiation (Giacomelli et al., 2003). This kind of molecules, containing  $\alpha$ -amino acid with rigid frameworks, are attractive synthetic targets since they can be used as conformationally restricted fragments in



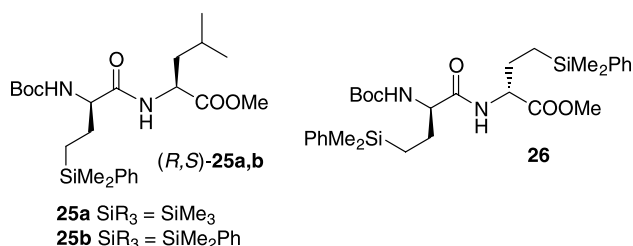
Scheme 9



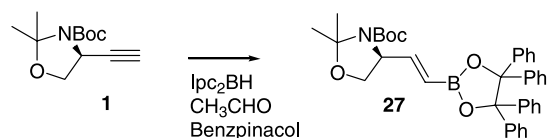
Scheme 10



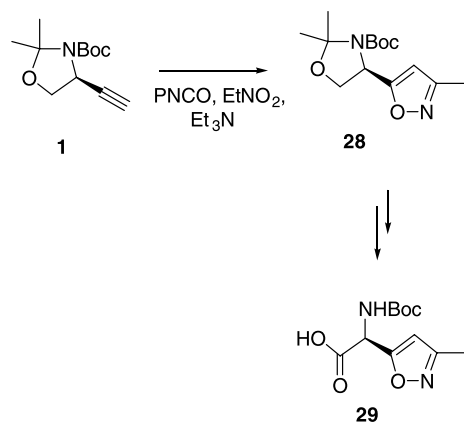
Scheme 11



**Fig. 5.** Silylated dipeptides obtained from silylated amino acids



**Scheme 12**



**Scheme 13**

the design of new peptidomimetic structures with biological activity.

## Conclusions

The use of readily available, enantiomerically pure starting materials has demonstrated its utility as a basis for enantiospecific synthesis. Our contribution in this area has been summarized introducing (R)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine (**1**) as a new, enantiomerically pure, starting material for the synthesis of new optically active amino acids and derivatives.

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