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MINIREVIEW ARTICLE

Ethynylglycine synthon, a useful precursor for the synthesis of biologically active compounds: an update

Part I: preparations of ethynylglycine synthon

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Abstract The ethynylglycine synthon {(*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine} is a chiral compound with valuable synthetic interest. An update on the different routes for its synthesis is reviewed and discussed.

Keywords Synthesis · Ethynylglycine synthon · Bestmann-Ohira · Corey-Fuchs

Abbreviations

Boc	*Tert*-butoxycarbonyl
Cbz	Benzyloxycarbonyl
DIBAL-H	Diisobutylaluminum hydride
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
Ts	4-toluenesulfonyl
ent-**x**	Enantiomer of compound **x**

Introduction and goals

Ethynylglycine synthon **1a** (Fig. 1) was reported for the first time, but independently, by us (Reginato et al. 1995; Meffre et al. 1995).

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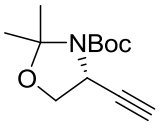
In 2005, we published a mini-review in this journal about the use of ethynylglycine synthon **1a** in the synthesis of non-natural amino acids (Reginato et al. 2005).

Nearly 10 years later, it is time to update the knowledge on the synthesis and use of 4-ethynyloxazolidine, showing the broad range of synthetic applications of this compound. Although some commercial sources are available, ethynylglycine synthon **1a** has usually to be prepared. Therefore, we will focus in the present review (part I) on the preparations of this compound (and its derivatives) described in the literature so far. The synthetic strategy adopted and the preferred protection for the amino protecting group will be discussed. Part II of this review will be devoted to the uses of ethynylglycine synthon in synthesis and will be published later.

Oxazolidine **1a** is prepared from Garner's aldehyde **2a** (Garner 1984; Garner and Park 1987; Meffre et al. 1994). For recent reviews on serinal derivatives of type **2**, see Passiniemi and Koskinen (2013) and Bera et al. (2013).

Two strategies have been used. In the first one, oxazolidine **1a** is prepared from **2a** via direct aldehyde-to-alkyne one carbon homologation using dimethyl 1-diazo-2-oxopropylphosphonate **3** (Bestmann–Ohira reagent, diazo strategy, method A) (Fig. 2; Ohira 1989). This method is also reported as Seyferth–Gilbert strategy.

The second strategy is a two steps sequence via dibromovinyl intermediate (Corey–Fuchs strategy, method B) (Fig. 2; Corey and Fuchs 1972). Table 1 gives an overview of all the methods used in the literature to prepare ethynylglycine synthon **1a**. Whenever possible, yield, scale, information on synthetic protocols detailed in the paper as well as the specific rotation of **1a** are reported in Table 1.



1a

Fig. 1 (*R*)-2,2-dimethyl-3-(tertbutoxycarbonyl)-4-ethynyloxazolidine {ethynylglycine synthon}

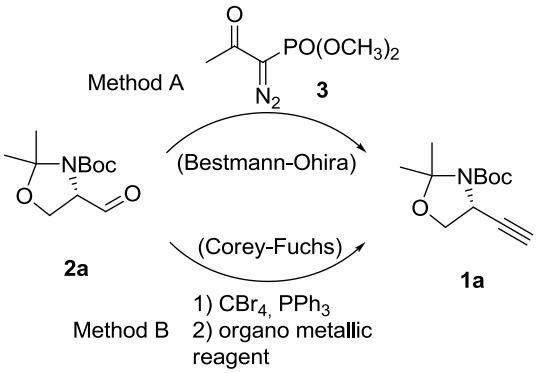


Fig. 2 The two strategies to synthesize ethynylglycine synthon **1a**

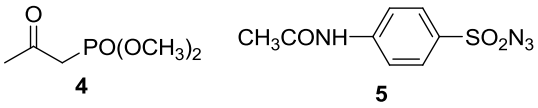


Fig. 3 The starting materials for in situ synthesis of **1a** from **2a** (Meffre et al. 2002)

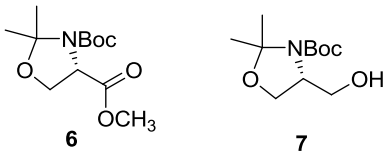


Fig. 4 Precursors for aldehyde **2a**

Ethynylglycine synthon synthesis using Bestmann–Ohira strategy (method A)

Because the conditions required to prepare Bestmann–Ohira reagent **3** are compatible with the aldehyde-to-alkyne transformation procedure, we have improved the reported synthetic methods, describing a simple one-pot multicomponent process (Meffre et al. 2002) for the preparation of **1a** from aldehyde **2a**. This involves the in situ formation of dimethyl 1-diazo-2-oxopropylphosphonate **3** from commercially available phosphonate **4** and diazo transfer reagent **5** (Fig. 3). Although the reaction seems to be slower with 4-acetamidobenzenesulfonyl azide **5** compared to the usually reported tosyl azide (TsN3), the former was preferred as diazo transfer reagent. Being a crystalline solid, it is easier to manipulate and to prepare in a pure form, and is known not to exhibit impact properties.

Garner aldehyde **2a** can be obtained either by ester reduction or alcohol oxidation, and should be possibly used without purification to avoid a possible racemization. This was shown by Pietruszka et al. (2003) which used crude aldehyde **2a** obtained either by reduction of ester **6** using DIBAL-H, or by oxidation of alcohol **7** using Dess–Martin periodinane (Fig. 4) together with Bestmann–Ohira reagent **3**.

The aldehyde-to-alkyne homologation can be performed directly starting from aldehyde precursors too: ester **6** (Branquet et al. 1993) and alcohol **7** (Meffre et al. 1994) (Fig. 4). Taking advantage of the mild nature of Bestmann–Ohira reaction, Dickson et al. (2004) reported a two step one-pot synthesis of *ent*-**1a** using strategy A with methyl ester *ent*-**6** as starting material, non-isolated intermediate aldehyde *ent*-**2a** being obtained by DIBAL-H reduction.

Belanger et al. (2009) used alcohol **7** as starting material which was oxidized into aldehyde **2a** using TEMPO (no specific rotation is given for intermediate **2a**). The aldehyde was directly engaged in the aldehyde-to-alkyne homologation. However, the specific rotation of alkyne **1a** obtained in this way is reported to be much lower compared to other procedures which could be interpreted as a loss in enantiomeric purity during TEMPO oxidation.

Ethynylglycine synthon synthesis using Corey–Fuchs strategy (method B)

When the Corey–Fuchs strategy (Method B) is used, a dibromovinyl intermediate **8** is generated in the first step of the reaction which is reacted with BuLi to give the corresponding alkyne (Fig. 5). Variable amounts of enamine **9a** are always formed in this transformation. This byproduct is generally present in very small amounts (lower than

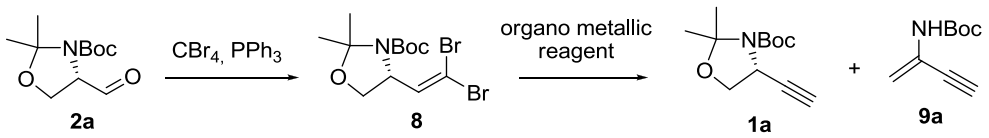


Fig. 5 The Corey-Fuchs strategy (method B). Degradation product **9a** observed in the preparation of **1a** (variable amounts)

10 %) and became predominant only when a large excess of base was used for prolonged reaction times (Reginato et al. 1995, 1997; Meffre et al. 1995, 1996; Branquet et al. 1998).

The use of a Grignard reagent as base in the second step proved to be better than BuLi, minimizing ring degradation and formation of enyne **9a**. Erdsack and Krause (2007) showed that use of propylmagnesium chloride gave excellent yields, proving to be even more convenient than the Bestmann–Ohira reagent (method A). Analogously, Yamakawa et al. (2010, 2011) used ethylmagnesium bromide.

This strategy has also been used in the synthesis of both enantiomers of α-ethynylalanine (Avenoza et al. 1999).

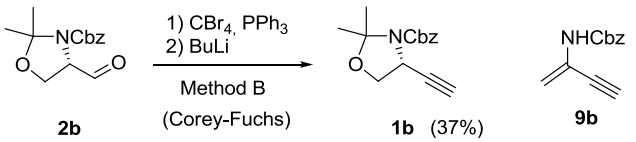


Fig. 6 Preparation of Cbz-protected ethynylglycine synthon **1b** (Reginato et al. 1998)

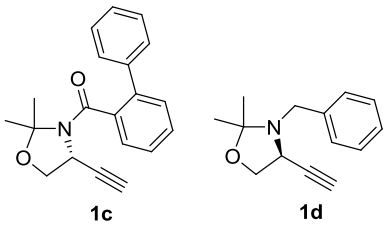


Fig. 7 Ethynylglycine synthons with *o*-phenylbenzoyl (**1c**) or benzyl (**1d**) as a *N*-protecting group (Ayed et al. 2010a, b)

The amino protecting group issue

Reginato et al. (1998) enlighted the role of the amino protecting group in the Corey–Fuchs strategy (method B) using BuLi as base. While enyne **9a** can be formed in variable amounts with Boc protected oxazolidine **2a** (Garner's aldehyde), formation of enyne **9b** was never observed in the reaction mixture when Cbz protecting group was used. Thus, **1b** was obtained from **2b** using method B, however, the transformation proved to be less efficient (Fig. 6).

Ayed et al. (2010a) described the synthesis of **1c** using *o*-phenylbenzoyl group as a *N*-protecting group (Fig. 7). This was necessary as the Boc group was not compatible with indium(0)-mediated coupling reaction of alkynyl iodide **10** which gave cyclic compound **11** because of Boc participation, instead of the *C*-glycosylated derivative **12**. In this case, the authors proposed a reduction with indium(0) of the carbamate moiety in **10** followed by a cyclization on the triple bond activated by indium(I) to give **11** (Fig. 8).

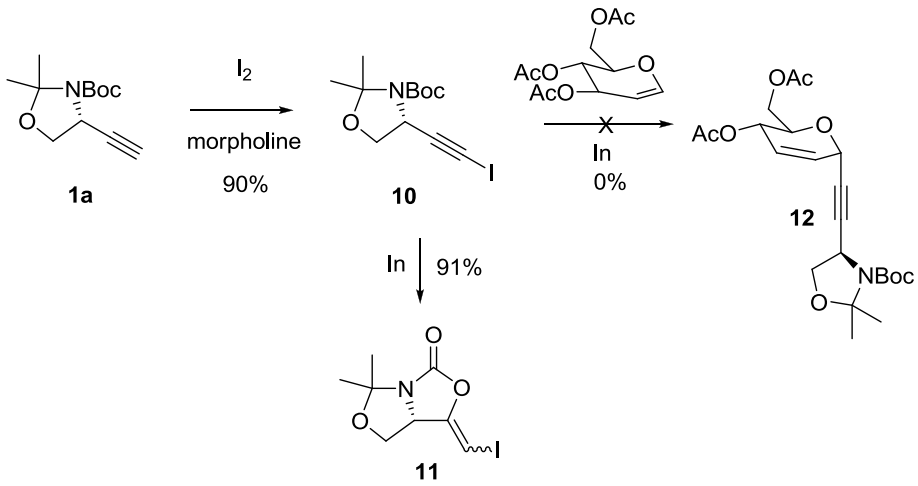


Fig. 8 Indium mediated reduction of carbamate and cyclization (Ayed et al. 2010a)

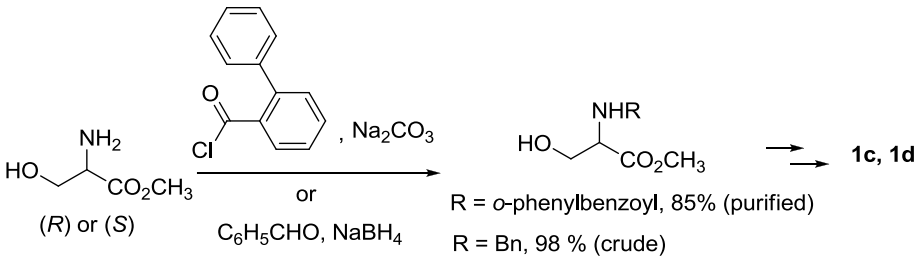


Fig. 9 Introduction of *o*-phenylbenzoyl and benzyl *N*-protecting groups for the syntheses of **1c** and **1d** (Ayed et al. 2010a, b; Barco et al. 1992)

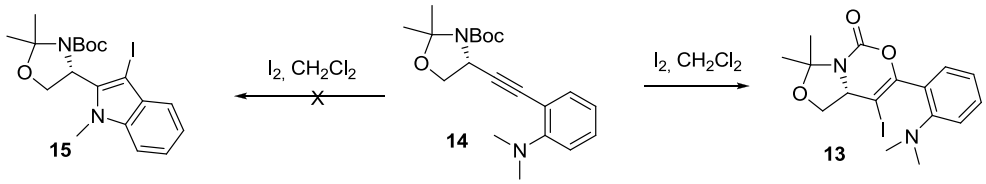


Fig. 10 Nucleophilic attack of Boc group under Larock's iodocyclization condition

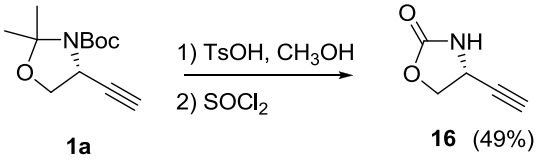


Fig. 11 Synthesis of ethynyloxazolidinone **16** from ethynylglycine synthon **1a**

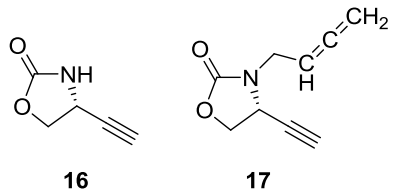


Fig. 12 4-Ethynyloxazolidin-2-one derivatives **16** and **17** as ethynylglycine synthons

The same group described also ethynyloxazolidine **1d** with a benzyl amino protecting group (Ayed et al. 2010b; Fig. 7). The synthesis of **1c** and **1d** are described from L- or D-serine methyl ester hydrochloride in good overall yield and full analyses are given (Ayed et al. 2010a, b; Barco et al. 1992; Fig. 9).

Again, the participation of Boc protecting group (nucleophilic attack) under Larock's iodocyclization conditions (I_2, CH_2Cl_2) was reported by Goswami et al. (2012b). In this case compound **13** was formed from **14** instead of expected indole derivative **15** (Fig. 10).

To solve this problem, ethynylglycine synthon **1a** was transformed into ethynyloxazolidinone **16**, through the removal of acetonide protection and reaction of the resulting amino alcohol with thionyl chloride (experimental details and analyses are given for this compound) (Fig. 11).

Synthesis of 2-indolylglycine derivatives using Sonogashira coupling followed by cyclization was then possible using ethynyloxazolidinone **16** as starting material.

In the oxazolidinones family, allenyne **17** was also obtained from the corresponding aldehyde using Bestmann–Ohira reagent (method A) (Kumareswaran et al. 2004; Fig. 12). This compound represents an advanced intermediate for the synthesis of highly functionalized pyrrolidines such as kainic acids or its congeners.

It is worth to highlight, however, that alkynes **1a-d**, **16** and **17** seem to be the only optically active cyclic ethynylglycine synthon derivatives described in the literature so far.

It should be also remarked that nucleophilic substitution at alkoxide of amino alcohol derived from oxazolidine ring opening is strongly dependent on the amino protective

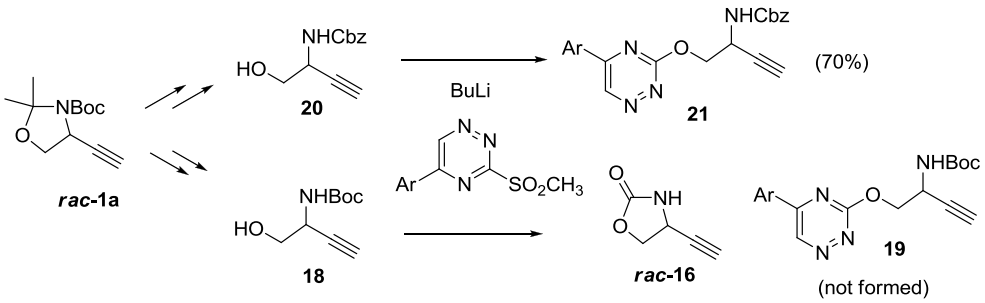


Fig. 13 Different behavior of ethynylglycine synthon derivatives protected with Boc or Cbz groups towards nucleophilic substitution (Ar is an aromatic substituent)

Fig. 14 Synthesis of alkynes **22** and **23**

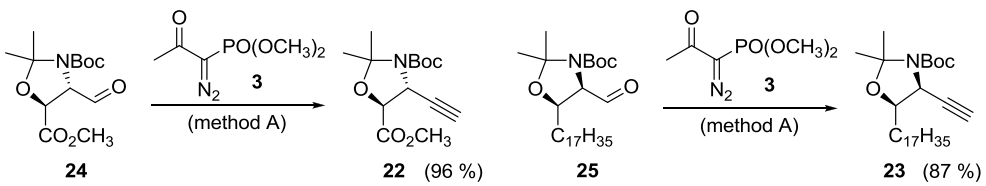


Table 1 Overview of all the methods used in the literature to prepare ethynylglycine synthon **1a**

Year of pub.	Abs. config. of **1a**	Ref.	Method for **1a** preparation (A or B, Fig. 2)	Yield in **1a** from **2a** (unless otherwise noted) (%)	Detailed or specific protocole in the ref.	Scale for **1a** (g; mmol)	Ref. cited for preparation	Comments	Specific rotation for **1a**
2013		(Goswami et al. 2013)	A		No		(Crisp et al. 1997)		
2013		(Alcaide et al. 2013)	A		No		(Bélanger et al. 2009; Spangenberg et al. 2010)		
2013		(Kimura et al. 2013)	A		No		(Pietruszka et al. 2003)	Reference for preparation: see supporting info in (Kimura et al. 2013)	
2012		(Goswami et al. 2012a, b)	A		No		(Crisp et al. 1997; Meffre et al. 1996)		
2012	*(S)*	(Usuki et al. 2012)	A	83	Yes	1.05; 4.65	(Meffre et al. 2002)	Experimental: see supporting info in (Usuki et al. 2012)	$[\alpha]_D^{20} = +90.9$ ($c = 0.1$, $CHCl_3$)
2012		(Raji Reddy et al. 2012)					?		
2011		(Kavitha et al. 2011)	?				?		
2010		(Ayed et al. 2010b)	A	67	No		(Meffre et al. 2002)		
2010	*(S)*	(Yamakawa et al. 2010, 2011)	B	86	Yes	5.74; 25.5	(Erdsack and Krause 2007)	EtMgBr as organometallic reagent	$[\alpha]_D^{22} = +81$ ($c = 1$, $CHCl_3$)
2010	*(S)*	(Spangenberg et al. 2010)	A	71	Yes	0.7; 3.1	(Meffre et al. 2002)		$[\alpha]_D^{20} = +96.6$ ($c = 1$, $CHCl_3$)
2010	*(R)*	(Ayed et al. 2010a)	A	67	Yes	1.3; 6	(Meffre et al. 2002)		?
2010		(Temperini et al. 2010)	A		No		(Meffre et al. 1996)		
2009	*(R)*	(Bélanger et al. 2009)	A	67[a]	Yes	0.652; 3	(Meffre et al. 1996)	[a]Yield from alcohol precursor which is oxidized into aldehyde by TEMPO	$[\alpha]_D^{20} = -1$ ($c = 1.25$, $CHCl_3$)
2009		(Stecko et al. 2009)	A		No		Method from Müller et al. (1996)[b]	In this reference[b], a general protocole is given	
2009		(Badarau et al. 2009)	A	84	No		(Meffre et al. 1996)		Racemic
2008		(Brummond and Yan 2008)	A	61	No		(Crisp et al. 1997; Meffre et al. 1996, 1995)		Racemic
2007	*(R)*	(Erdsack and Krause 2007)	B	70	Yes	8.1; 36	(Cameron and Khambay 1998)	*n*-PrMgCl or *n*-PrMgBr as organometallic reagent	In agreement with Crisp et al. (1997)
2007	*(S)*	(Govek and Overman 2007)	A	86	Yes	16; 71	(Meffre et al. 1996)	Experimental: see supporting info in (Govek and Overman 2007)	Not reported
2007		(Lin and Kazmaier 2007)	A		No		(Meffre et al. 1995)		

Table 1 continued

Year of pub.	Abs. config. of **1a**	Ref.	Method for **1a** preparation (A or B, Fig. 2)	Yield in **1a** from **2a** (unless otherwise noted) (%)	Detailed or specific protocole in the ref.	Scale for **1a** (g; mmol)	Ref. cited for preparation	Comments	Specific rotation for **1a**
2006		(Guillarme et al. 2006)	B		No		(Reginato et al. 1995)		
2006		(Reginato et al. 2006)	B		No		(Reginato et al. 1995)		
2005		(Pulley et al. 2005)	A		No		(Ohira 1989)		
2005		(Reginato et al. 2005)	B		No		(Reginato et al. 1997)		
2005		(Yanada et al. 2005)	A		No		(Serrat et al. 1999)		
2004	*(S)*	(Dickson et al. 2004)	A	71[c]	Yes	1; 4.4	(Dondoni et al. 2001)	[c]Yield from methyl ester ester precursor which is reduced into aldehyde by DIBAL-H	$[\alpha]_D^{20}$ =+93 (c = 0.018, $CHCl_3$)
2003	*(R)*	(Pietruszka et al. 2003)	A	58[d] and 64[e]	Yes	7; 31	(Meffre et al. 1995, 2002; Crisp et al. 1997)	Crude aldehyde is treated with Bestmann–Ohira reagent.[d]Yield from alcohol precursor which is oxidized into aldehyde by Dess-Martin periodinane.[e]Yield from ester precursor which is reduced into aldehyde by DIBAL-H	$[\alpha]_D^{23} = -90.2$ (c = 2.63, $CHCl_3$)
2002	*(R)*	(Meffre et al. 2002)	A	72	Yes	0.154; 0,7	(Meffre et al. 1995, 1996; Reginato et al. 1995; Crisp et al. 1997; Reginato et al. 1997)	One-step synthesis of **1** using in situ formation of dimethyl 1-diazo-2-oxopropyl phosphonate	$[\alpha]_D^{20} = -99$ (c = 0.96, $CHCl_3$)
2002	*(S)*	(Meffre et al. 2002)	A	69	Yes	1.55; 7		Id	$[\alpha]_D^{20}$ =+102 (c = 1.02, $CHCl_3$)
2001	*(S)*	(Dondoni et al. 2001)	A		No		(Serrat et al. 1999)		$[\alpha]_D^{20}$ =+90 (c = 0.7, $CHCl_3$)
2000		(Callahan et al. 2000)	A		No		(Meffre et al. 1995)		
1999		(Pulley et al. 1999)	A		No		(Meffre et al. 1995)		
1999	*(R)*	(Serrat et al. 1999)	A	79	Yes	9.34; 42	(Reginato et al. 1995, 1997; Meffre et al. 1996)		$[\alpha]_D^{20} = -88.2$ (c = 1.05, $CHCl_3$)
1998		(Cameron and Khambay 1998)	B		No		(Meffre et al. 1996; Reginato et al. 1997)		
1998		(Falorni et al. 1998)	B	62	No		(Reginato et al. 1997)		
1997	*(R)*	(Reginato et al. 1997)	B	79	Yes	0,482; 2	(Meffre et al. 1995; Reginato et al. 1995)		$[\alpha]_D^{20} = -73.5$ (c = 1.01, $CHCl_3$)

Table 1 continued

Year of pub.	Abs. config. of **1a**	Ref.	Method for **1a** preparation (A or B, Fig. 2)	Yield in **1a** from **2a** (unless otherwise noted) (%)	Detailed or specific protocole in the ref.	Scale for **1a** (g; mmol)	Ref. cited for preparation	Comments	Specific rotation for **1a**
1997	(*S*)	(Reginato et al. 1997)	B	58	Yes	0.047; 0.2	(Meffre et al. 1995; Reginato et al. 1995)		$[\alpha]_D^{20}$ =+75 (*c* = 1.03, $CHCl_3$)
1997	(*R*)	(Crisp et al. 1997)	A	78	Yes	1.53; 6.8	(Reginato et al. 1995, 1997)		$[\alpha]_D^{20}$ = −81.3 (*c* = 2.43, $CHCl_3$)
1996	(*R*)	(Meffre et al. 1996)	A	80	Yes	1,97; 8.7			$[\alpha]_D^{20}$ = −96.5 (*c* = 1.23, $CHCl_3$)
1995		(Meffre et al. 1995)	A	75–85	No				
1995	(*R*)	(Reginato et al. 1995)	B	74	Yes	0.057; 0.25			$[\alpha]_D^{20}$ = −75.5 (*c* = 1, $CHCl_3$)
1995	(*S*)	(Reginato et al. 1995)	B						$[\alpha]_D^{20}$ =+75 (*c* = 1.03, $CHCl_3$)

Whenever possible, yield, scale, information on synthetic protocols detailed in the paper as well as the specific rotation of **1a** are reported

group, especially if potential leaving groups are present. This is illustrated in Fig. 13, where methylsulfonyl group substitution gave the formation of an oxazolidinone ***rac*-16** as a side product when carried out on Boc derivative **18** instead of Boc derivative **19**. This is due to cyclization of the alkoxide derived from **18**. However, it proved to be possible to perform the reaction using Cbz protected amino alcohol **20** yielding to Cbz derivative **21** (Badarau et al. 2009). The authors highlighted the importance "to try different protecting groups of the amine moiety that did not incorporate potential leaving group in their structures" (Badarau et al. 2009). This can be explained by a difference in leaving group ability of *tert*-butoxide group compared to benzyloxide group which favour an internal nucleophilic attack in the case of Boc group leading to **rac-16**. Both compounds **18** and **20** are derived from racemic ethynylglydine synthon ***rac*-1a**.

Note in addition

Alkynes **22** and **23**, closely related to ethynylglycine synthon **1a** were synthesized from their aldehyde precursors **24** and **25**, respectively, using method A in very good yields (Fig. 14; Debnar et al. 2013; McDonagh and Murphy 2014, respectively).

Conclusion

Six optically active cyclic ethynylglycine synthons **1a–d**, **16** and **17** have been described in the literature. The most popular is the ethynyloxazolidine **1a** with Boc as amino protecting group. It has been prepared from serine via Garner aldehyde **2a** as key intermediate, the alkyne being obtained from the aldehyde either directly using Bestmann–Ohira reagent or the two steps Corey–Fuchs transformation. Several protocols have been described in the literature for both methods and have been collected in Table 1. The best should be probably selected depending on the synthetic application desired. Protection of the amino group might be a crucial issue as shown in many cases. Particularly, the Boc group might have an influence (participation) in the synthesis of **1a** but also can play an important role when this chiral synthon is used in multistep synthesis (see part II).

Conflict of interest The authors declare that they have no conflict of interest.

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