Amino Acids (2018) 50:1307–1328
https://doi.org/10.1007/s00726-018-2628-1

INVITED REVIEW

Ethynylglycine synthon, a useful precursor for the synthesis of biologically active compounds: an update. Part II: synthetic uses of ethynylglycine synthon

Zohra Benfodda[1] · David Benimélis[1] · Gianna Reginato[2] · Patrick Meffre[1]

Received: 11 June 2018 / Accepted: 20 July 2018 / Published online: 11 August 2018

Abstract
The ethynylglycine synthon {(R)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyl-oxazolidine} is a chiral compound with valuable synthetic interest. An update (covering literature from 2005 to 2017) on the different synthetic utilities is reviewed and discussed.

Keywords Synthesis · Ethynylglycine synthon · Terminal alkyne · Metallation · Metal-catalyzed coupling · Cycloaddition

Abbreviations

Ac	Acetyl
ACC synthase	1-Aminocyclopropane-1-carboxylate synthase
All	Allyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu or *n*-Bu	*n*-Butyl
CAN	Cerium ammonium nitrate
Cbz	Benzyloxycarbonyl
dba	Dibenzylideneacetone
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DIBAL-H	Diisobutylalumino hydride
DIPA	Diisopropylamine
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
ent-**x**	Enantiomer of compound **x**
Et	Ethyl
HMDS	Hexamethyldisilazane
IDO	Indoleamine 2,3-dioxygenase
LHMDS	Lithium bis(trimethylsilyl)amide
MCPBA	*m*-Chloroperoxybenzoic acid
Me	Methyl
Mts	2,4,6-Trimethylbenzenesulfonyl
MW	Microwave
NCS	*N*-Chlorosuccinimide
*o*DPPBA	2-(Diphenylphosphino)benzoic acid
*o*DPPB	2-(Diphenylphosphino)benzoate
Ph	Phenyl
PLP	Pyridoxal phosphate
PTSA	*p*-Toluenesulfonic acid
RCM	Ring-closing metathesis
SEM	2-(Trimethylsilyl)ethoxymethyl
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
t-Bu	*tert*-butyl
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
TES	Triethylsilyl
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethyl ethylenediamine
TMS	Trimethylsilyl
Ts	4-toluenesulfonyl

Handling Editor: J. D. Wade.

✉ Patrick Meffre
patrick.meffre@unimes.fr

[1] UNIV. NIMES, EA7352 Chrome, Rue du Dr G. Salan, 30021 Nîmes Cedex 1, France

[2] ICCOM—CNR, Via Madonna del Piano 1, 50019 Sesto Fiorentino, Italy

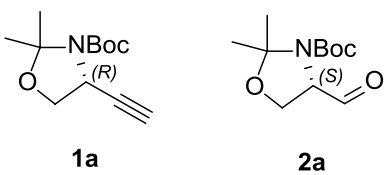
Introduction and goals

In 2015, we decided to update the knowledge on ethynylglycine synthon **1a** since our latest review in 2005 (Reginato et al. 2005b). The recently published part I of this review (Benfodda et al. 2015) dealt with the preparations of this compound (and its derivatives) from Garner's aldehyde **2a** described in the literature so far (Fig. 1). The synthetic strategy adopted, the optical purity, and the preferred protection for the amino protecting group have been discussed there. The present part II of this review will be devoted to the uses of ethynylglycine synthon in synthesis that have been reported since our 2005 review (2005–2017), showing the broad range of recent synthetic applications of this polyfunctional chiral synthon.

The data that appeared after 2005 and that were not cited previously by us in our 2005 review (Reginato et al. 2005b) will be developed in this review; the previous references already cited in the 2005 review will only be cited in the paragraph headings, but the chemistry will not be developed. While writing this part II review, we noticed that a limited number of results earlier than 2005 were not developed in our 2005 review (Reginato et al. 2005b), that is why they now appear in the present review.

In neighbouring topics, it should be pointed out that Jirgensons recently published a review on the methods for the synthesis of α-ethynylglycines derivatives described since 1996 (Bolsakova and Jirgensons 2016), the precedent review being our older report on β,γ-alkynyl α-amino acids. (Meffre and Le Goffic 1996). We also published recently a comprehensive review on synthesis of α-quaternary α-ethynyl α-amino acids (Boibessot et al. 2016b).

Due to the presence of the oxazolidine ring (used especially as a synthetic precursor of α-amino acids) and of the terminal alkyne moiety, that allows several synthetic transformations, ethynylglycine synthon **1a** is a useful building block for the synthesis of compounds of biological interest. The review will be organized considering the reaction type performed on the terminal alkyne (Fig. 1).



1a **2a**

Fig. 1 (*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyl-oxazolidine {ethynylglycine synthon} **1a** and Garner's aldehyde **2a**

Metallation and reaction with electrophiles (Reginato et al. 1995, 1997; Meffre et al. 1996; Serrat et al. 1999; Cabarrocas et al. 2000a, b, 2001; Dondoni et al. 2001)

Electrophile is an aldehyde

Historically, this reaction was the first to be reported in the field of ethynylglycine synthon chemistry, in 1990. Because the Corey–Fuchs strategy (Benfodda et al. 2015) from aldehyde *ent*-**2a** yields to ethynylglycine synthon lithium acetylide **(Li$^+$)-*ent*-1a**, the latter was directly trapped with paraformaldehyde to give a propargyl alcohol derivative **3** (Chung and Wasicak 1990). This compound was further functionalized to lead to an oxotremorine analogue **4**. Oxotremorine **5** is the active metabolite of tremorine, a muscarinic receptor agonist (Fig. 2).

Compound **3** was also used in 2010 to obtain the allenic oxazolidine **7** via a copper-mediated ortho-(diphenylphosphanyl)benzoate (*o*DPPB)-directed S_N2' reaction with an excellent regioselectivity (S_N2'/S_N2 = 95/5) (Fig. 3) (Spangenberg et al. 2010).

The lithium acetylide derived from **1a** was also reacted to TBDMS protected salicylaldehyde to give alcohol **8** (no yield given) which was then subjected to a one-pot acid-catalyzed nucleophilic substitution, fluoride TBDMS desilylation and exo-dig cycloisomerization to 2,3-disubstituted benzofuran **10** (Raji Reddy et al. 2012) (Fig. 4). It is worth noting that $B(C_6F_5)_3$ was used as acid catalyst instead of $BF_3.Et_2O$ because of the presence of acid labile acetonide group in **8**.

The lithium acetylide derived from *ent*-**1a** was again used and converted to an alkynyl zinc reagent in the presence of excess zinc chloride, necessary to ensure a highly selective addition to aldehyde **11** in favor of the formation of the 1,2-*syn* alkoxide **12**, followed by a ring opening of the epoxide activated by excess Lewis acid zinc chloride. α-*C*-(ethynylglycine)-galactoside **13** was thus obtained (Guillarme et al. 2006) (Fig. 5).

Electrophile is a carboxylate or an isocyanate

The lithium acetylide derived from *ent*-**1a** was also condensed with methylchloroformate (inverse addition method to avoid the formation of enyne due to deprotonation and acetone elimination) to obtain alkynoate *ent*-**14**. Hydrostannylation followed by Stille cross coupling with iodo tryptophan **16** and NBoc deprotection led to the synthesis of **17**. Compound **17** is a precursor to (+)-asperazine, an alkaloid with cytotoxic activity against human leukemia (14 steps from *ent*-**1a**) (Govek and Overman 2007) (Fig. 6).

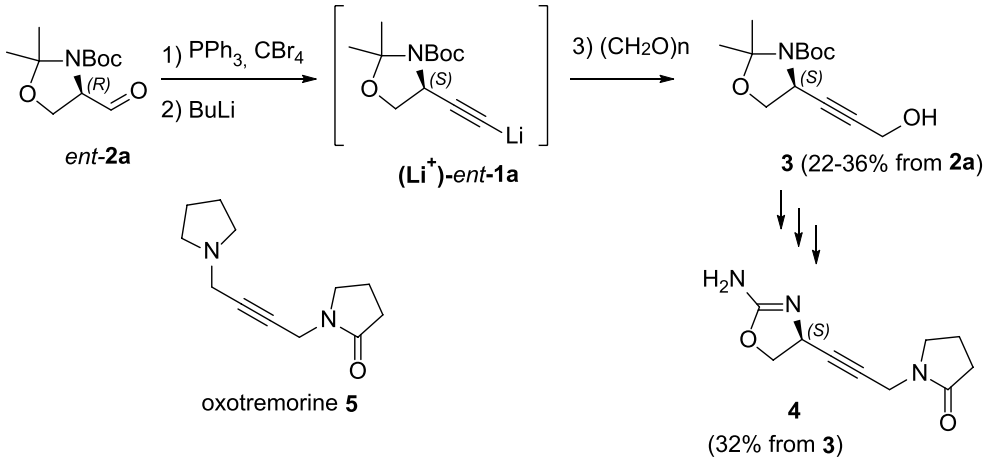


Fig. 2 Synthesis of the oxotremorine analogue **4**

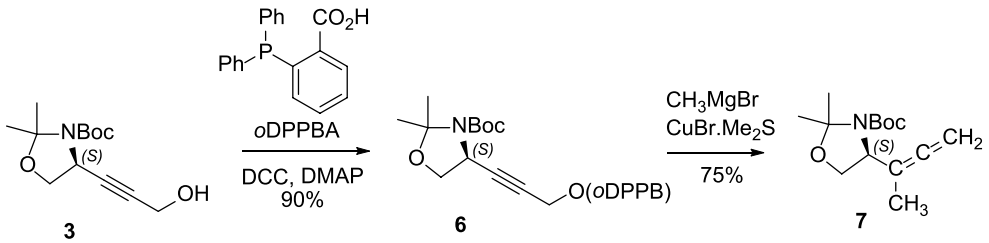


Fig. 3 Synthesis of the allenic oxazolidine **7** via S_N2' reaction

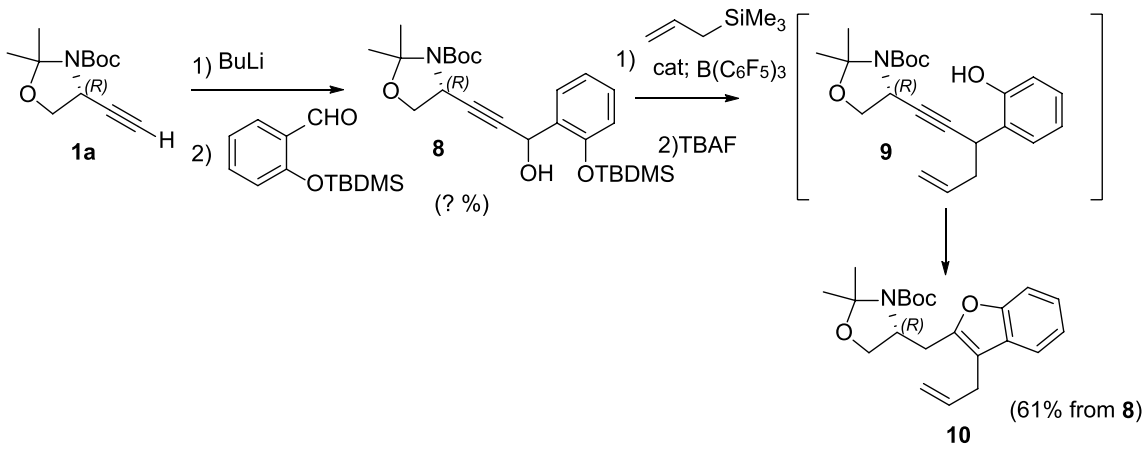


Fig. 4 Synthesis of the 2,3-disubstituted benzofuran **10**

The alkynoate **14** (obtained by condensation of the lithium acetylide derived from **1a** with methyl cyanoformate, Mander's reagent) was also engaged in a cycloaddition with benzyl formhydroximate **18** to afford isoxazole **19** which is a precursor of isoxazole **20** (9 steps from **1a**). Isoxazole **20** is the precursor of a tetracycline core structure (11 steps from 20) (Wzorek et al. 2012) (Fig. 7).

The arylamide **22**, also obtained by condensation of the lithium acetylide derived from **1a** with isocyanate **21,** was subjected to an In-mediated radical cyclization to yield oxindole **24**, a possible precursor of TMC-95A, a naturally occurring proteasome inhibitor (Yanada et al. 2005) (Fig. 8). Indeed, looking at the configuration of the starting material **1a** used by the authors, and at the configuration of the

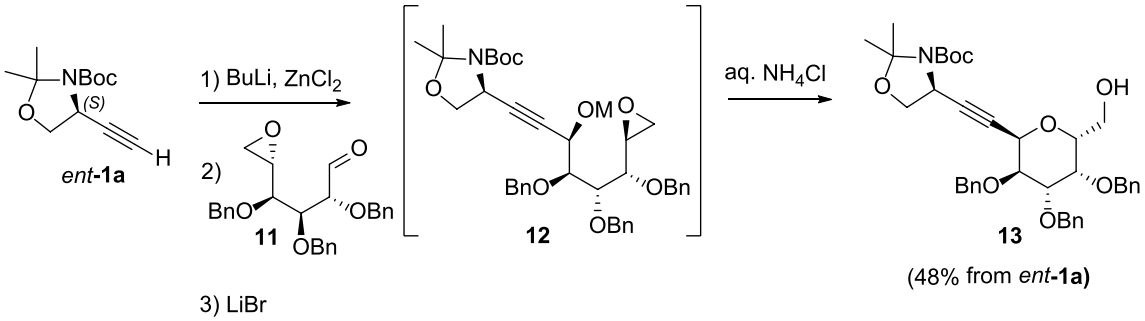


Fig. 5 Synthesis of the α-*C*-(ethynylglycine)-galactoside **13**

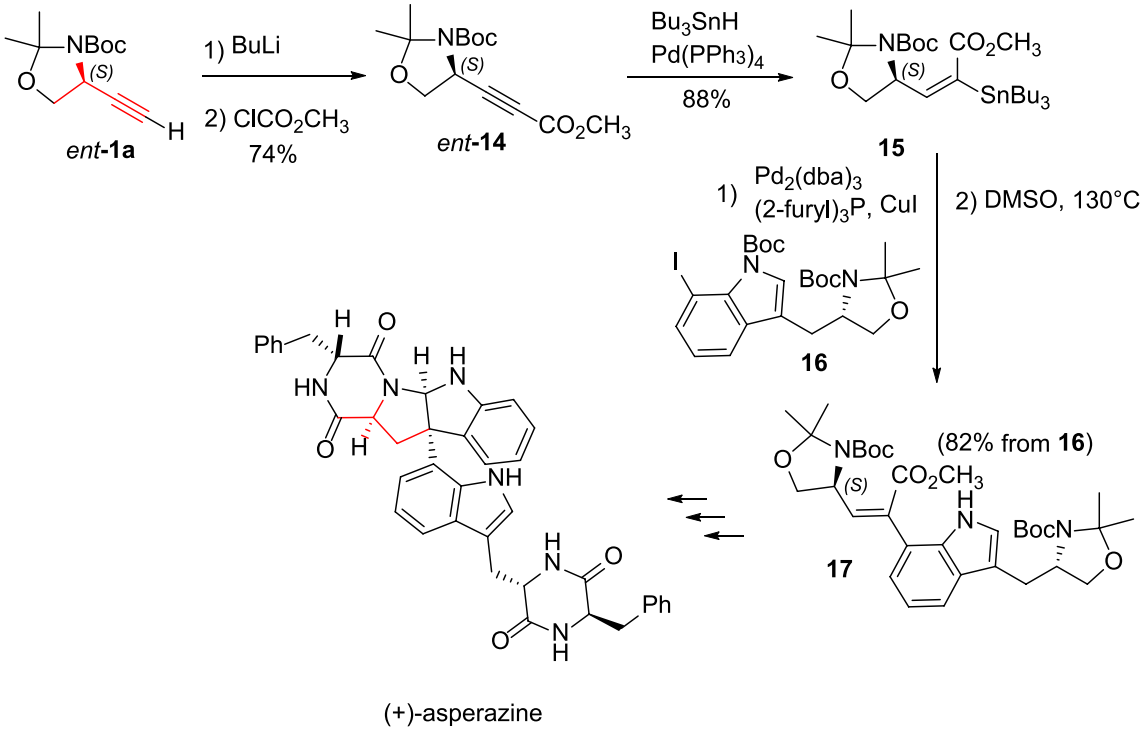


Fig. 6 Synthesis of methyl enoate **17**, precursor of (+)-asperazine

stereogenic carbon 8 in TMC-95A, it seems that using (*R*)-**1a** oxindole (*R*)-**24** would be actually obtained, which is a precursor of a diastereoisomer of TMC-95A (Fig. 8).

Electrophile is an alkyl halide

Some time ago, our groups reported the synthesis of silylated amino acids using the ethynylglycine synthon (Meffre et al. 1996; Reginato et al. 1998, 1999). More recently, we described the synthesis of unsaturated amino acids containing an allyl silane moiety (Reginato et al. 2006), using a silylated alkyl halide as electrophile, the amino acid being obtained from the oxazolidine ring by oxidation (Fig. 9).

Finally, ethynylglycine synthon rac-**1a** was converted to cyclic carbamate **29**. The terminus of the alkyne in **29** was functionalized with trimethyl silyl and phenyl groups to give **30** and **31** which were subjected to an allenic Alder-ene reaction to give unstable triene **34** and **35** (Brummond and Yan 2008) (Fig. 10).

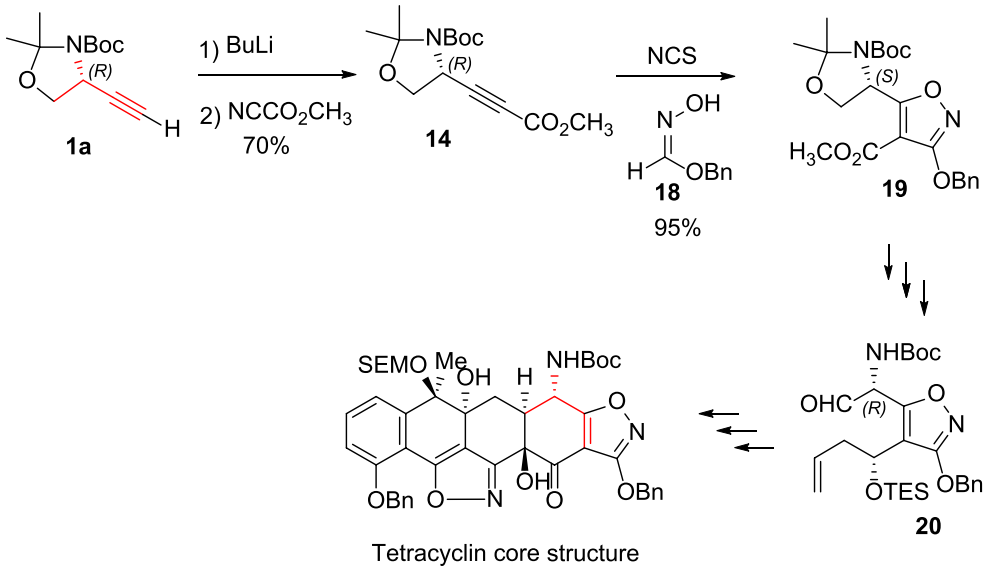


Fig. 7 Synthesis of isoxazole **20**, precursor of a tetracyclic core structure

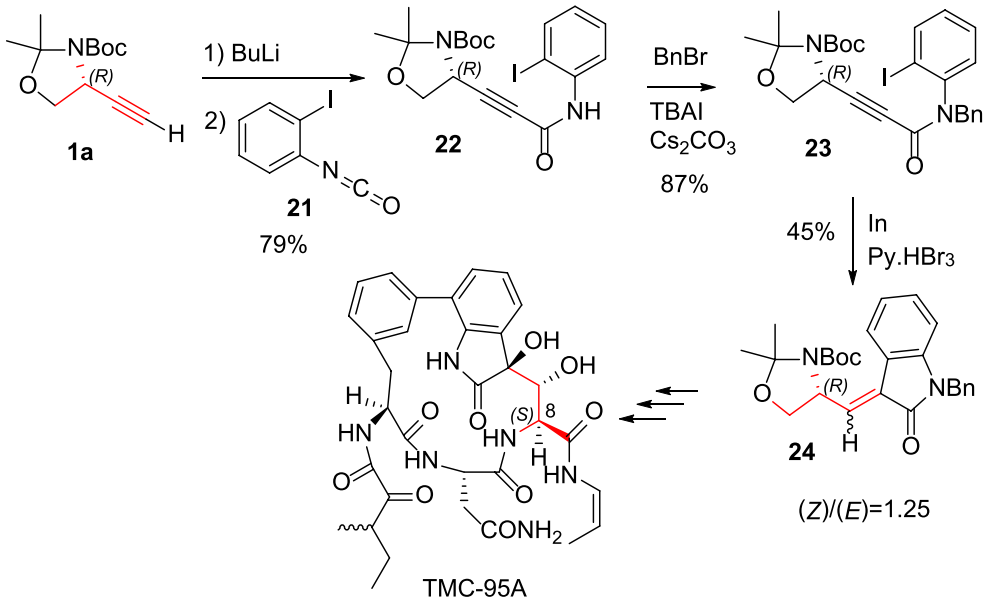


Fig. 8 Synthesis of oxindole **24**, precursor of TMC-95A

Pd-catalyzed coupling reactions: Sonogashira couplings (Reginato et al. 1997; Crisp et al. 1997; Cameron and Khambay 1998)

The terminal alkyne moiety on ethynylglycine synthon **1a** allows functionalization using the well-known Pd-catalyzed Sonogashira coupling reaction (Chinchilla and Nájera 2007).

Furanomycin **41** is an unusual amino acid containing a 2,5-dihydrofuran ring that presents antibiotic activity (Katagiri et al. 1967; von Nussbaum et al. 2006) (Fig. 11).

The 2,5-dihydrofuran ring in the furanomycin analogue **40** was synthesized using a gold-catalyzed cycloisomerization of α-hydroxyallene **38** as the key step to obtain the precursor bicyclic dihydrofuran **39**. α-Hydroxyallene **38** is obtained from propargyl oxirane **37** by a copper-mediated S_N2'-substitution. Propargyl oxirane **37** is prepared from the corresponding enyne **36** which is obtained in turn from

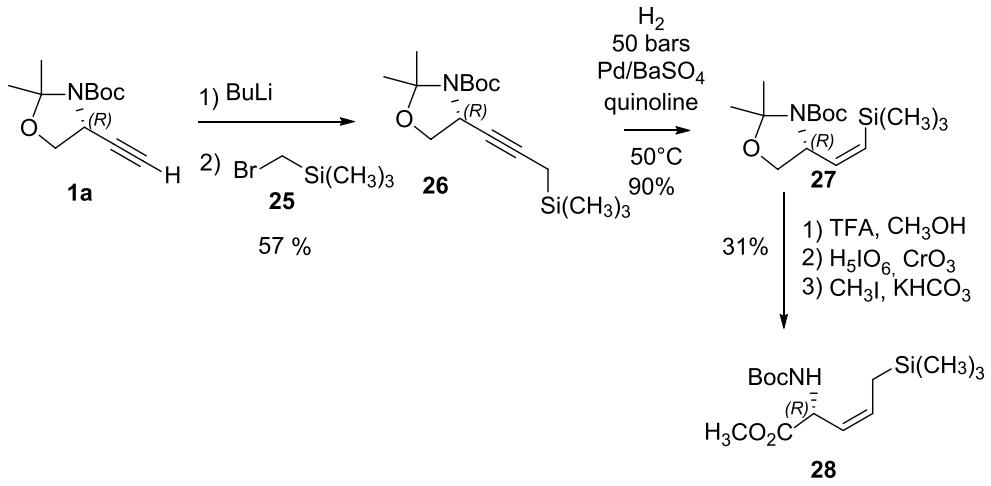


Fig. 9 Synthesis of an allylsilane amino acid derivative **28**

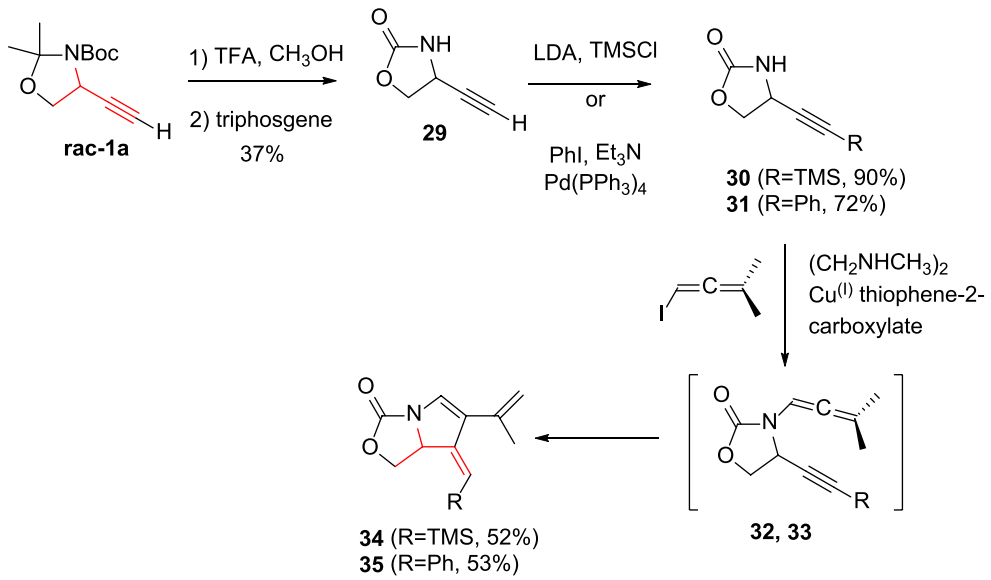


Fig. 10 Synthesis of conjugated trienes **34** and **35**

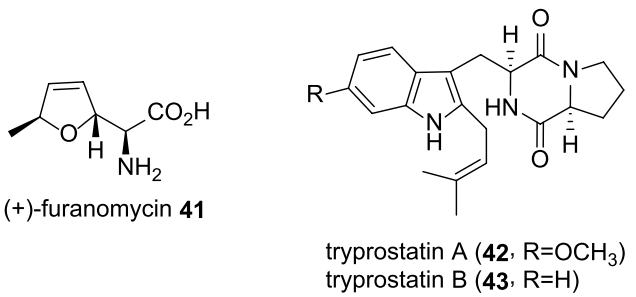


Fig. 11 Structures of (+)-furanomycin **41** and tryprostatins A **42** and B **43**

ethynylglycine synthon **1a** by a Sonogashira coupling with 1-bromocyclooctene (Fig. 12) (Erdsack and Krause 2007).

Tryprostatins A (**42**) and B (**43**) are naturally occurring 2,3-disubstituted indoles that present antimitotic properties (Fig. 11) (Evidente et al. 2014).

Total synthesis of tryprostatin B (Fig. 13) starts with Sonogashira coupling of the aromatic iodide **45** on the terminal alkyne of *ent*-**1a**. After partial reduction and dehydration, ortho-alkenyl isocyanide **47** is obtained. The 2,3-disubstituted indole **49** is obtained from **47** in a one-pot process by a radical cyclisation using V70

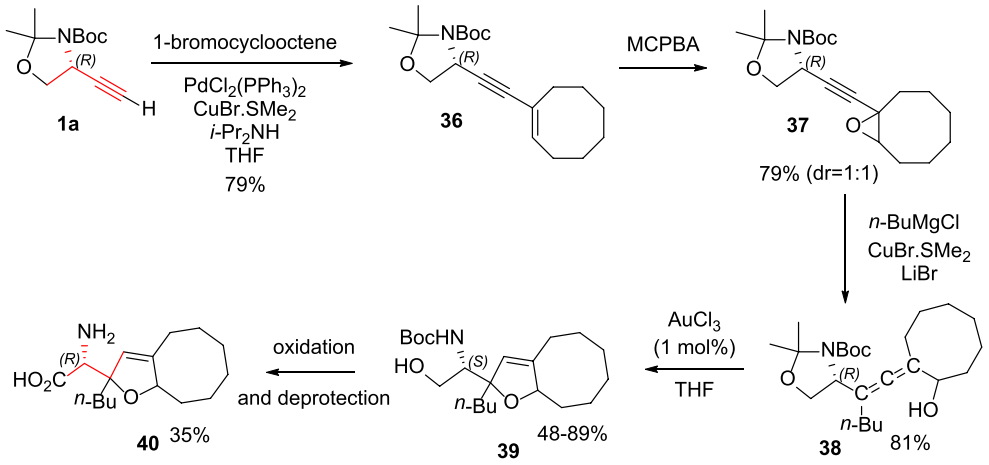


Fig. 12 Synthesis of furanomycin analogue **40**

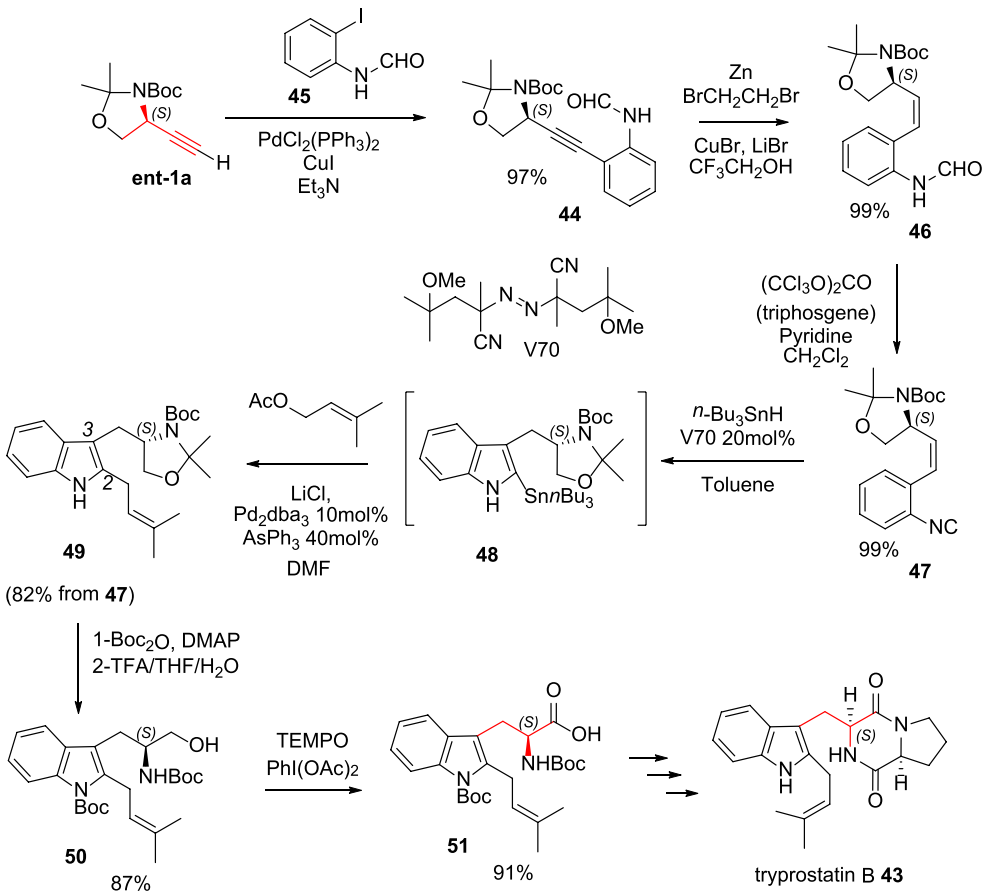


Fig. 13 Synthesis of carboxylic acid **51**, precursor of tryprostatine B **43**

(2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) as a radical initiator, followed by a Stille-type coupling reaction through the 2-stannyl indole intermediate **48**. After protection/deprotection steps and oxidation, compound **51**, key intermediate in the synthesis of tryprostatin B, is obtained. (Yamakawa et al. 2010, 2011, 2014). Tryprostatin A is obtained using the same strategy.

Tryptophan analogues are interesting compounds, because they are possible indoleamine 2,3-dioxygenase (IDO) inhibitors and could have application in the

treatment of inflammatory and neurodegenerative diseases (Röhrig et al. 2010). N,O-protected D-Homotryptophan **58** and its sulfur analogue **57** have been synthesized by Sonogashira coupling between 3-iodoheteroarenes and ethynylglycine synthon **1a** followed by reduction of the alkyne, oxidation of the alcohol, and esterification using diazomethane (Fig. 14) (Goswami et al. 2012b). The selenohomotryptophan **59** (Fig. 14) was synthesized by the same group using the same route (Goswami et al. 2013).

The same group described the synthesis of 2- and 3-indolylglycine derivatives and of their oxygen analogues using ethynylglycine synthon **1a** as starting material. Indolylglycines are interesting scaffolds which are present in bis-indole alkaloids like dragmacidins and hamacanthins (Goswami et al. 2012a).

3-Indolylglycine **68** and its oxygen analogue derivative **69** (Fig. 15) were prepared starting from the internal silyl derivatives **60** and **61** in turn obtained from **1a** using the literature procedure (Meffre et al. 1996). The key step is a

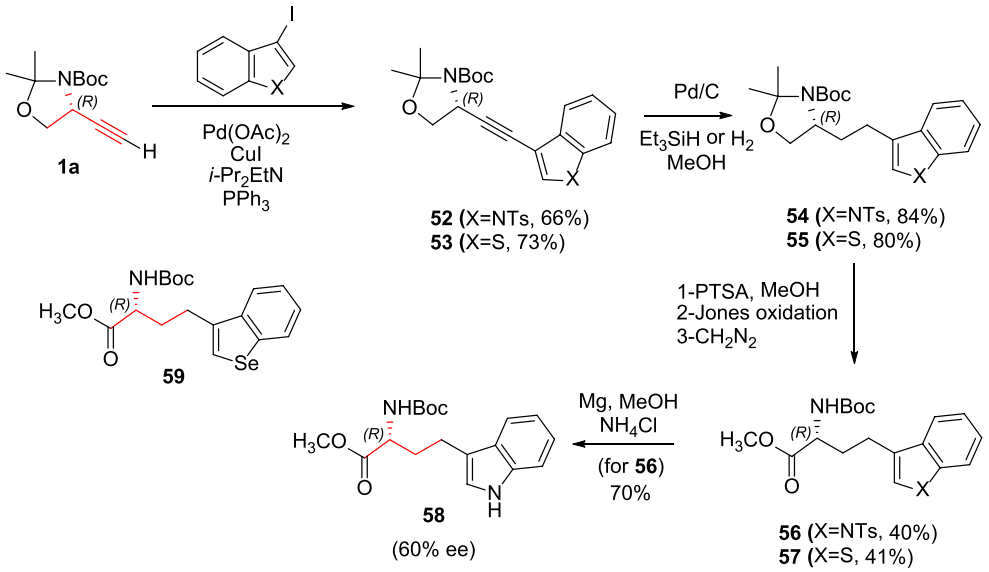


Fig. 14 Synthesis of homotryptophane derivative **58**

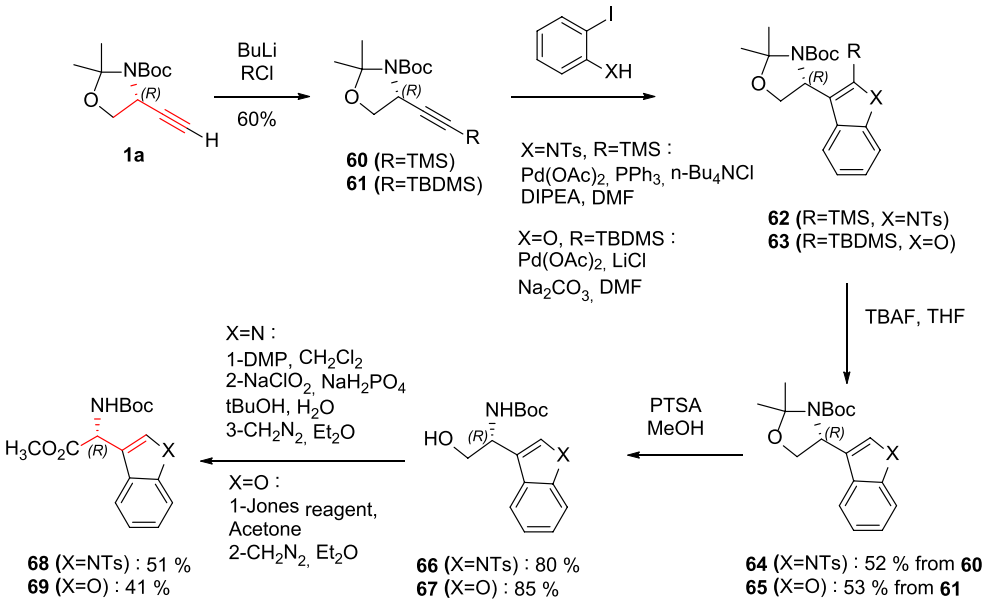


Fig. 15 Synthesis of 3-indolylglycine **68** and oxygen analogue **69**

Larock's heteroannulation with 2-iodoaniline and 2-iodophenol derivatives, to obtain compounds **62** and **63.** After desilylation and acid-catalyzed oxazolidine opening into N-Boc-protected amino alcohols **66** and **67**, the N,O-protected 3-indolylglycine **68** and the oxygen analogue **69** are obtained by oxidation and esterification (Goswami et al. 2012a).

Unfortunately, the synthesis of the 2-substituted indole derivatives using the same strategy failed, due to the incompatibility of Boc-protecting group. For example Larock's iodocyclization conditions (I_2, CH_2Cl_2) proved to be problematic because of Boc-protecting group participation (nucleophilic attack). In this case, compound **71** was formed instead of expected indole derivative **72** (Fig. 16) (Goswami et al. 2012a).

To solve this problem, ethynylglycine synthon **1a** was transformed into ethynyloxazolidinone **73**, through the removal of acetonide protection and reaction of the resulting amino alcohol with thionyl chloride (Fig. 17). Coupling of cyclic carbamate **73** under Sonogashira conditions gave compounds **74** and **75**, which after Boc protection and carbamate opening gave N-Boc-protected amino alcohols **76** and **77**, from which the N,O-protected 2-indolylglycine **78** and the oxygen analogue **79** are obtained by oxidation and esterification (Goswami et al. 2012a).

During the synthesis of the chronic obstructive pulmonary disease (COPD) biomarker (+)-desmosine **86**, a cross-linking amino acid of elastin, two of the four amino acid moieties present in the structure are introduced simultaneously using a Sonogashira cross-coupling

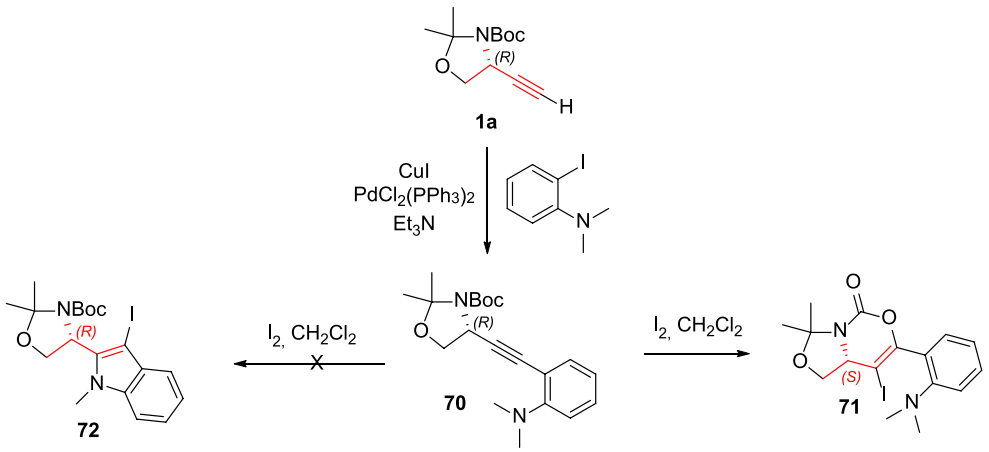


Fig. 16 Nucleophilic attack of Boc group under Larock's iodocyclisation condition: formation of cyclic carbamate **71** instead of indole **72**

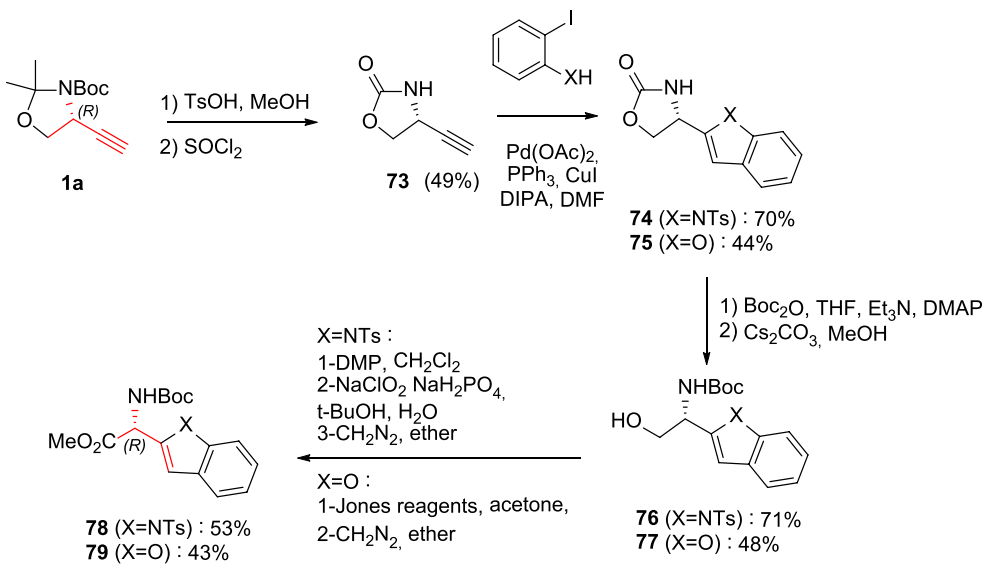


Fig. 17 Synthesis of 2-indolylglycine derivative **78** and oxygen analogue **79**

reaction on ethynylglycine synthon *ent*-**1a**, as a first step. Another Sonogashira coupling reaction using propargylglycine derivatives **81** introduces a third amino acid moiety. Hydrogenation and usual functional group transformations led to the pyridine derivative **83**, which is alkylated with the ω-iodobutylglycine derivative **84** to give N-Boc-protected desmosine **85**. (+)-desmosine **86** is obtained after deprotection (Fig. 18) (Usuki et al. 2012; Yamada et al. 2015).

Compound **88** was prepared by Sonogashira coupling between the ethynylglycine synthon *ent*-**1a** and triflate **87** and used to prepare 8-hydroxy-3-substituted isocoumarine **89** using a gold(I)-catalyzed cyclization (Fig. 19) (Mallampudi et al. 2017).

Cycloaddition reactions on the terminal alkyne (Falorni et al. 1998; Giacomelli et al. 2003)

The copper(I)-mediated reaction between nitrones and terminal alkynes (Kinugasa reaction) is a well-known method used for the β-lactam ring formation (Comas-Barceló and Harrity 2017). This reaction when applied to ethynylglycine synthon **1a** leads to the formation of lactam **91** only in traces, although the same reaction conducted on D-glyceraldehyde alkyne analogue **92** led to lactam **93** in 46% yield and with a good diastereoselectivity (Fig. 20) (Stecko et al. 2009).

The [3 + 2]-cycloaddition of alkynes with in situ generated difluoromethyl nitrile oxide **94** (obtained from oxime **95**) leads to CF_2H-isoxazoles. This reaction when applied

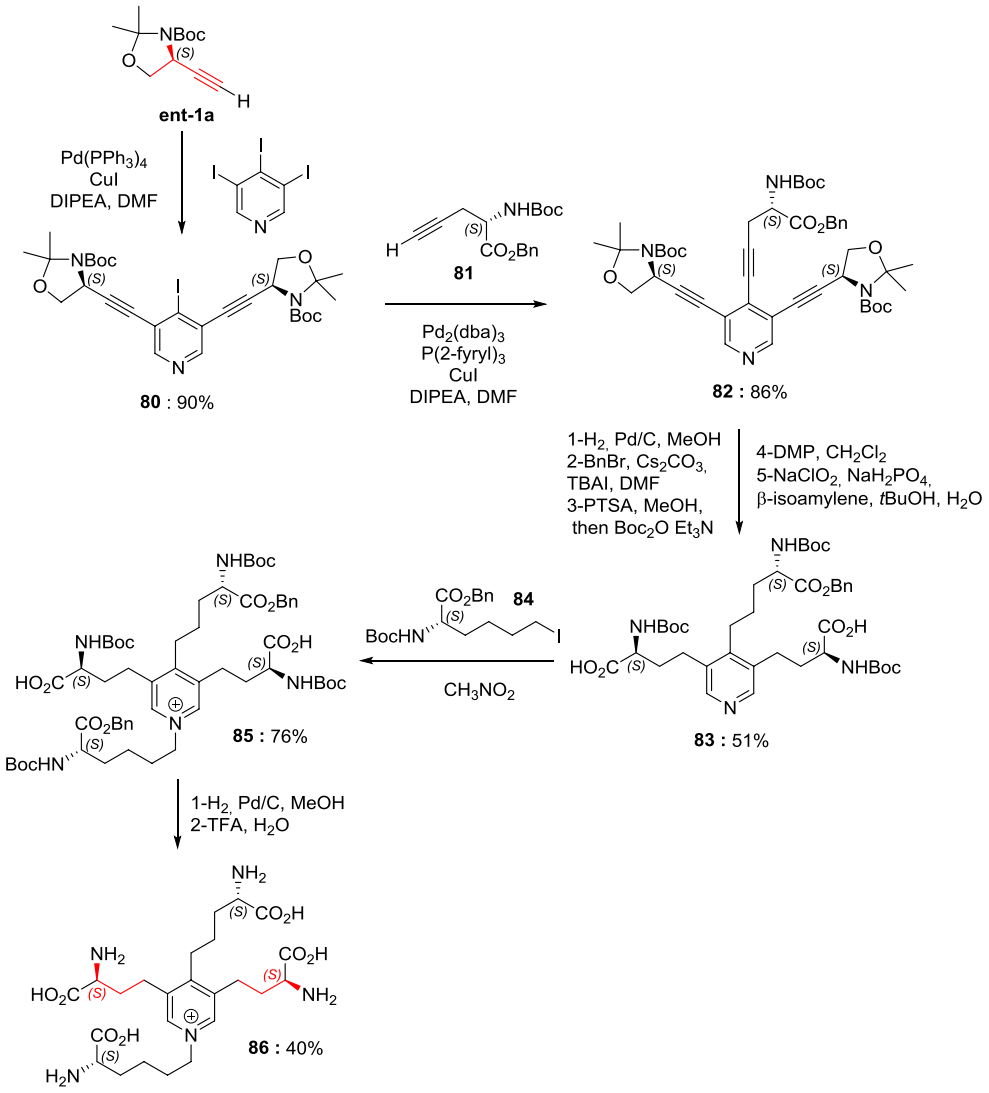


Fig. 18 Synthesis of (+)-desmosine **86**

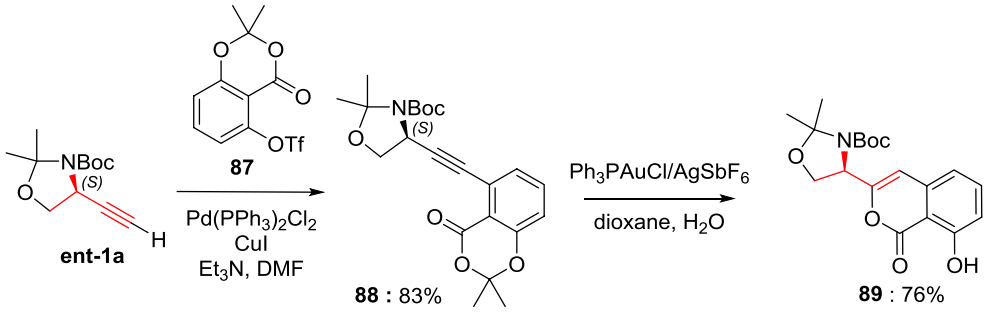


Fig. 19 Synthesis of isocoumarine derivative **89**

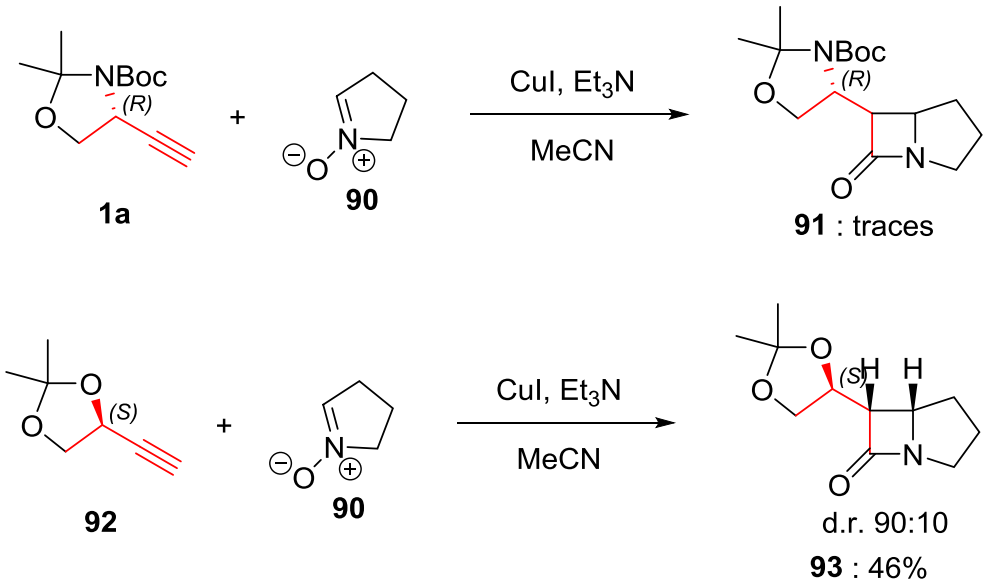


Fig. 20 Synthesis of β-lactams **91** and **93**

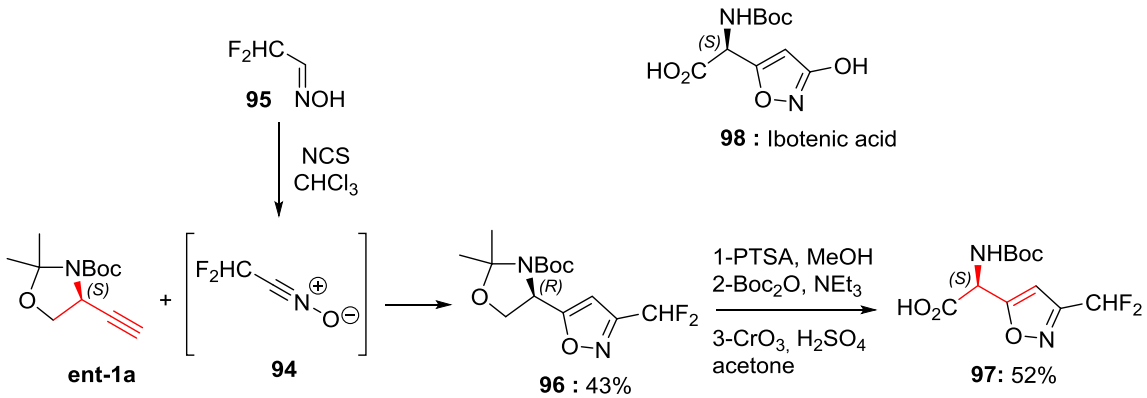


Fig. 21 Synthesis of isoxazole amino acid derivative **97**

to ethynylglycine synthon **ent-1a** lets to isoxazole **96**, a precursor of the fluorinated isoxazole amino acid **97** (Fig. 21) (Khutorianskyi et al. 2017). Due to bioisosterism of CHF_2 and OH groups, compound **97** is an analogue of ibotenic acid **98**, a naturally occurring non-selective glutamate receptor agonist. (Frydenvang et al. 2010).

For another similar reaction, see (Falorni et al. 1998; Giacomelli et al. 2003), already cited in our previous review (Reginato et al. 2005b).

Huisgen 1,3-dipolar cycloaddition of an alkyne and an azide is a well-known access to 1,2,3-triazoles (Huisgen 1963; Totobenazara and Burke 2015). *N*-styryl triazole **101** was obtained from ethynylglycine synthon **ent-1a** by Huisgen cycloaddition with azido styrene **99** (generated in situ from cinnamic acid **100**, CAN and NaN_3) (Kavitha et al. 2011) (Fig. 22).

Protected triazole amino acid **104** was also synthesized by us using the Huisgen cycloaddition of alkyne **102** and azido alanine **103** derived from L-serine. Protected aminoalcohol **102** was obtained by acid-catalyzed opening of the oxazolidine ring of ethynylglycine synthon **ent-1a**. Invertion of the deprotection/cycloaddition sequence led to lower yields (Boibessot et al. 2016a). Compound **104** is an analogue of rhizobitoxine **105**, a plant growth regulator and inhibitor of PLP-dependent enzymes cystathionine β-lyase and ACC synthase (Fig. 22) (Owens et al. 1968; Xiong and Fuhrmann 1996; Yasuta et al. 1999; Sugawara et al. 2006).

Arylglycines are an interesting class of unusual amino acids, because this moiety is present in the structures of important biologically active natural products (Mazuela et al. 2017).

These types of compounds have been prepared by Dötz benzannulation between Fischer chromium carbene complexes **106** and the alkyne functionality of the ethynylglycine synthon **1a** (Fig. 23) (Pulley et al. 1999, 2005).

In the key benzannulation reaction, the use of ultrasounds was found to improve yields.

The last oxidation step of arylglycinols **109** to arylglycines **110** proved to be problematic: the best results were obtained with a Dess–Martin oxidation followed by sodium chlorite oxidation using the Cbz-protecting group. The same oxidation performed on one of the Boc-protected arylglycinols proceeded in a lower yield (see, note 21 in Pulley et al. 2005).

Compounds **111** and **112** are serotoninergic chroman-based ligands with good activity (Fig. 24) (Holmberg et al. 2004, 2005). Badarau et al. synthesized compound **117**, the 3-amino-7-azabenzofuran analogue of **111** and **112,** starting from racemic ethynylglycine synthon **1a** (Badarau et al. 2009). After ring opening, substitution of the methyl sulfonate in triazine **114** gave **115** which, through an intramolecular hetero-Diels–Alder reaction between the triazine residue and the alkyne moiety, led to compound **116**. The reaction was carried out under microwave conditions using Cbz-protected alkyne **113**. It is worth noting that, due to the presence of a good leaving group, the same reaction led to the formation of an oxazolidinone when performed on Boc-protected amino alcool **102** (Fig. 22) (Badarau et al. 2009).

Finally, the cyclopropene glutamate analogue **120** was synthesized by an Rh-catalyzed cyclopropanation of ethyl diazoacetate and ethynylglycine synthon **1a** as a key step. Deprotection of oxazolidine **118** and oxidation of the alcohol finally furnished amino ester **120** although in low yield (Fig. 25) (Kumar et al. 2016). Ester deprotection proved to

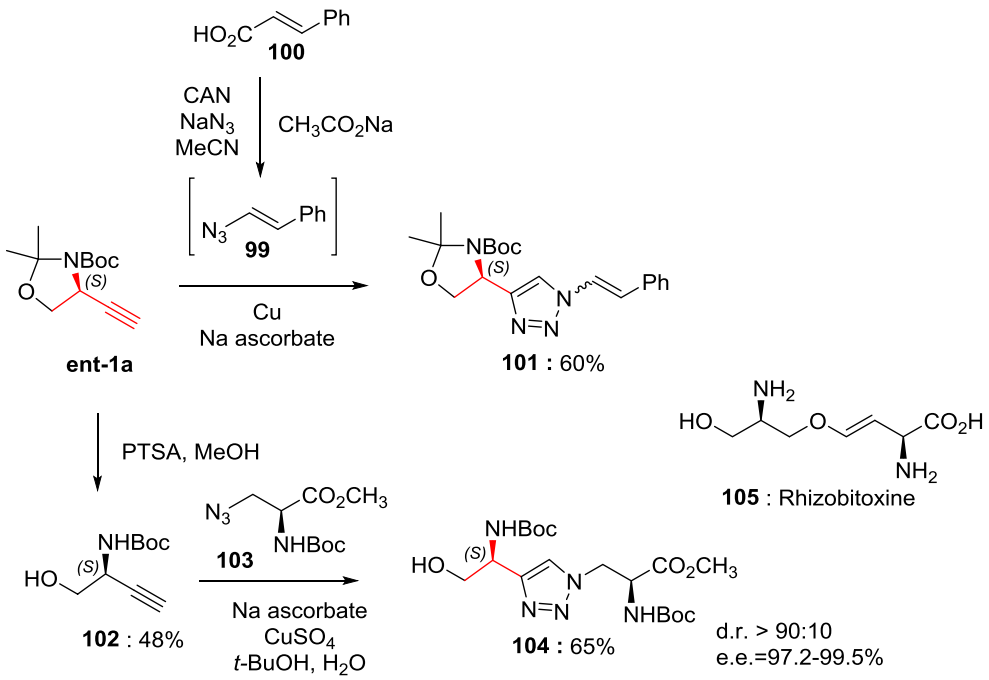


Fig. 22 Synthesis of triazole amino acid rhizobitoxine analogue **104**

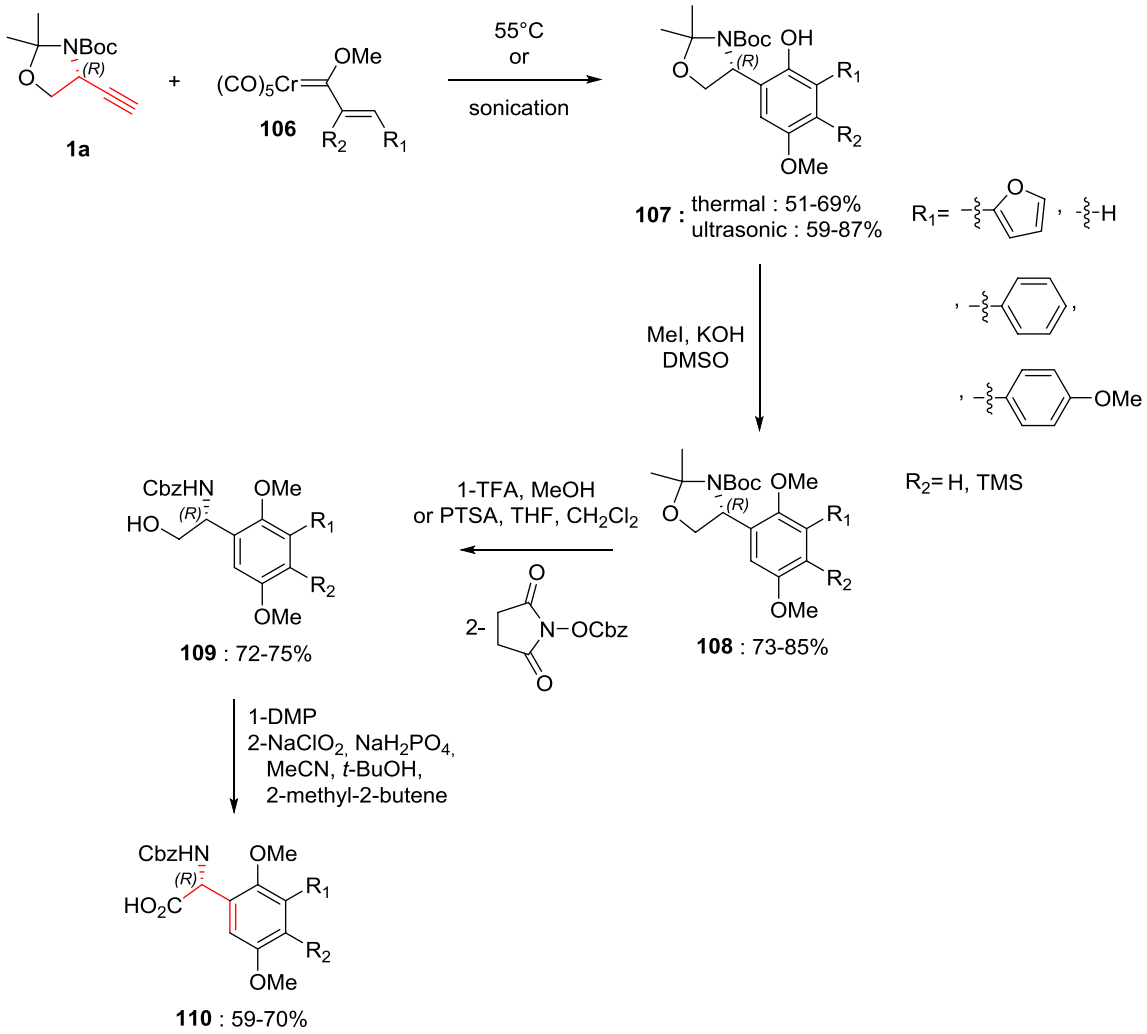


Fig. 23 Synthesis of arylglycine derivatives **110**

be unsuccessful. The unstability of these derivatives is due to the presence of the cyclopropene moiety and the acidic α-proton which lead to the formation of the corresponding allene (see supporting information in the reference of the work).

Addition of mixed tributylstannyl cuprate to the terminal alkyne and Stille coupling reactions (Reginato et al. 1997, 2000; Crisp et al. 1997)

Addition of stannylcuprate **121** onto ethynylglycine synthon **1a** gave the vinyl copper intermediate **122**. Hydrolytic work-up led to the γ-stannylated (E)-ethenyloxazolidine **123** in very good yield (Reginato et al. 1997).

Stille coupling with vinyl bromide gave diene **124**. The use of palladium acetate $Pd(OAc)_2$ and triphenylarsine $AsPh_3$ as ligand proved to be necessary to obtain diene **130** when 2-bromopropene is used.

Trapping the intermediate vinyl copper **122** with electrophiles gave β-substituted stannyl allylamines **125**, **126,** and **127**. Again Stille couplings led to diene **128** and triene **129** (Reginato et al. 2005a) (Fig. 26).

It is possible to obtain selectively the β-stannylated **131**, the regioisomer of **123** (**131/123** = 9:1), the two compounds being separated by chromatography, using hydrostannation of ethynylglycine synthon **1a** (Fig. 27) (Lin and Kazmaier 2007).

Compound **131** was subjected to Stille coupling reactions to afford alkenes **132** and **133**. Vinylketones **132** were used for Michael additions, while alkenes **133** led to protected aminoalcohols **135** after oxazolidine cleavage (in two steps).

This strategy was also used in the same paper to obtain chiral amino heterocycles by hydrostannation and ring-closing metathesis (RCM) (Fig. 28) (Lin and Kazmaier 2007).

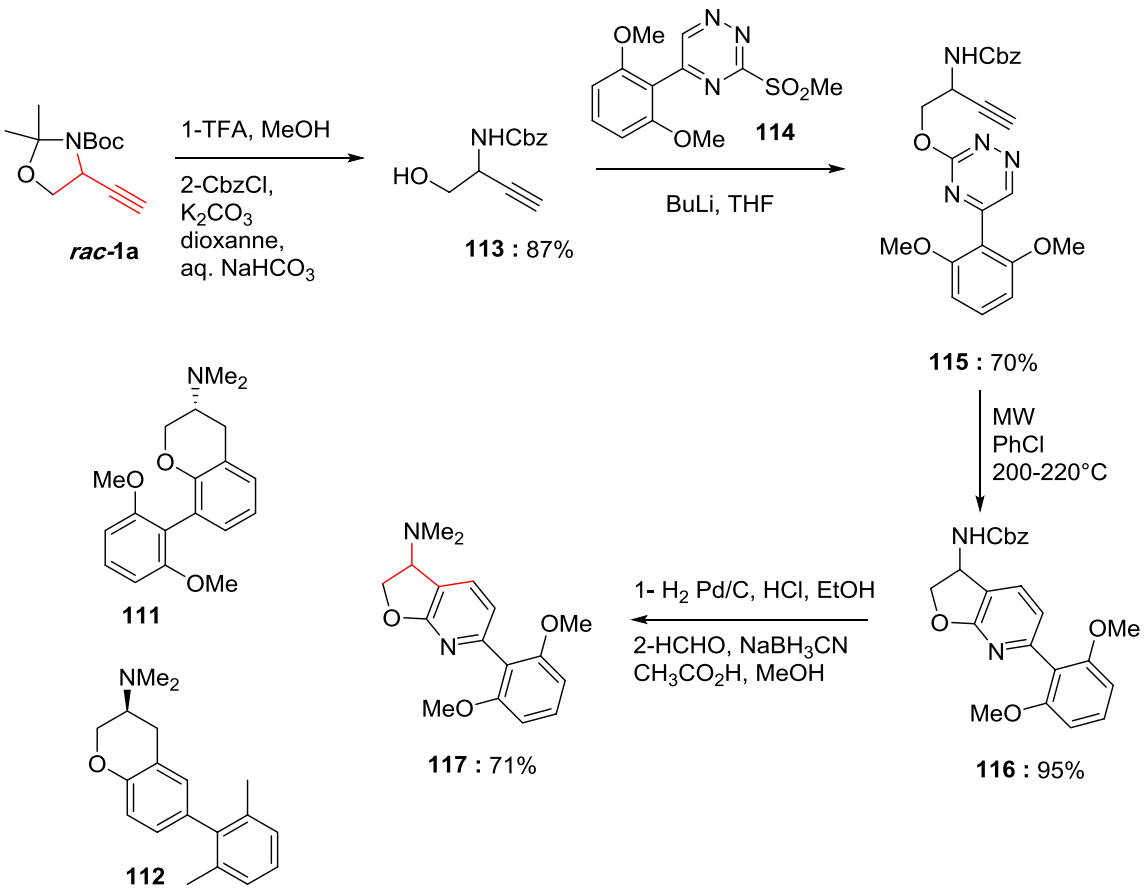


Fig. 24 Synthesis of a 3-amino-7-azabenzofuran derivative **117** analogue of serotoninergic ligands **111** and **112**

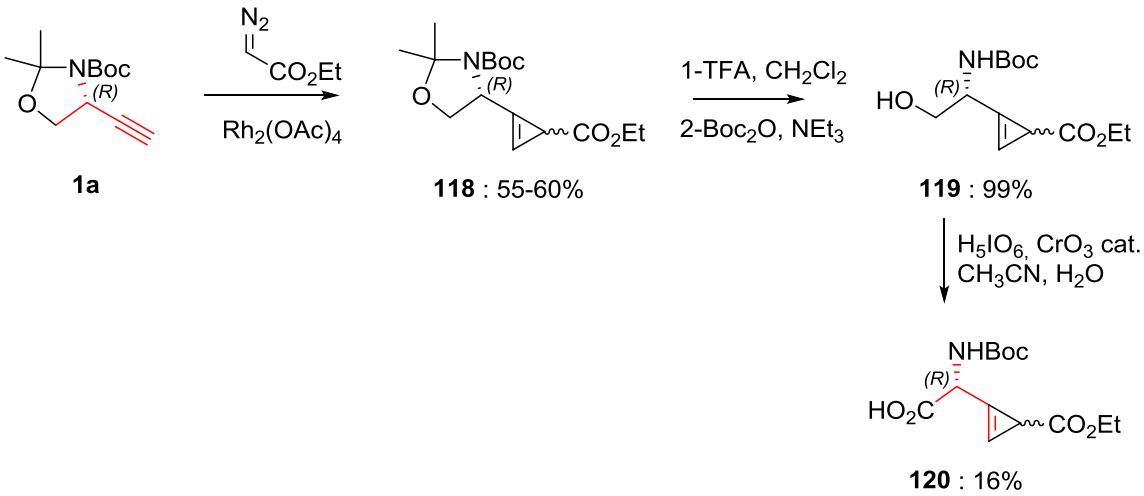


Fig. 25 Synthesis of a cyclopropene amino acid glutamate analogue derivative **120**

For this purpose, dienes **137** and **138** were needed. Because acidic cleavage of the oxazolidine ring could not be performed on the stannylated oxazolidine **131** (Fig. 27), alkyne **ent-102** was first obtained by acidic deprotection and hydrostannation was performed to give vinyl stannane **136** which was converted to dienes **137** and **138**.

Stille coupling and ring-closing metathesis led to heterocycles **141–142** and **147–148** (Fig. 28).

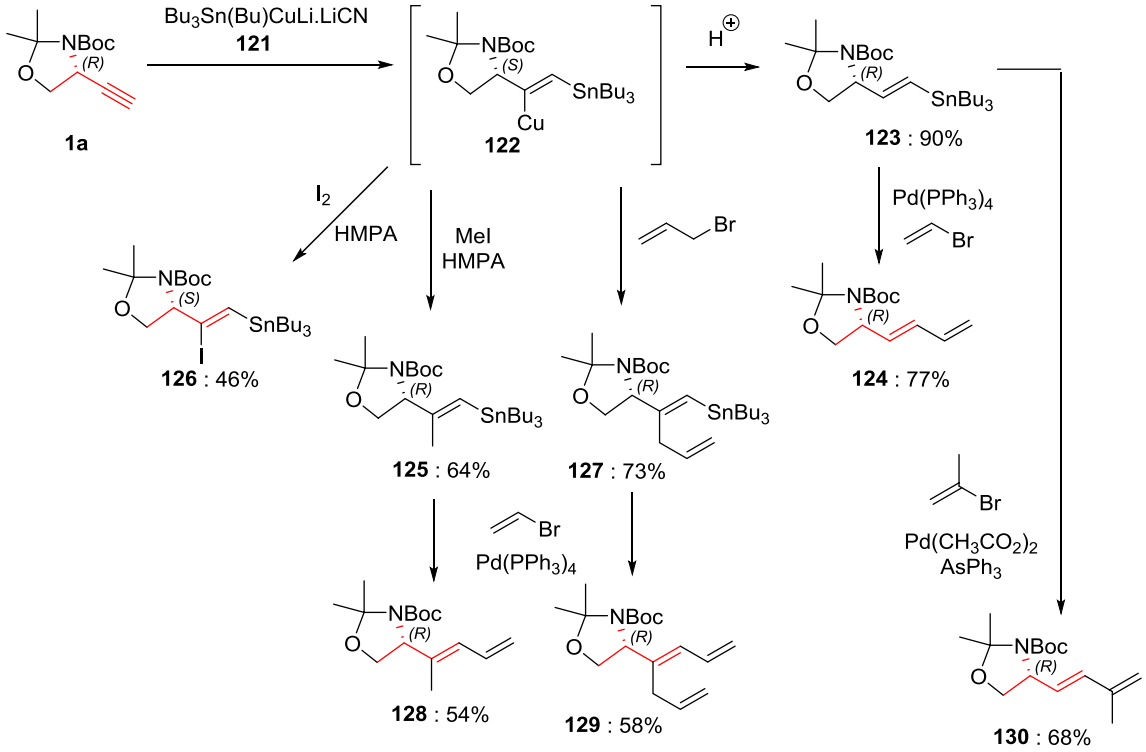


Fig. 26 Synthesis of diene and triene amino acid precursors **124**, **128**, **129,** and **130**

Metal-catalyzed C–C bond-forming reaction to the terminal alkyne (other than Pd-catalyzed couplings)

Enantiomerically pure N-Boc-protected (*R,R*)-diaminosuberic acid **152** was synthesized using a copper-catalyzed dimerization of ethynylglycine synthon **1a** as key step, followed by usual transformations (hydrogenation, deprotection, and oxidation). This strategy would allow a facile introduction of tritium or deuterium (Fig. 29) (Callahan et al. 2000).

It is possible to synthesize a *C*-glycosyl derivative using an indium-mediated alkynylation reaction between a glycal or sugar derivative and alkynyl iodides under Barbier conditions (Ayed et al. 2010a). This reaction, when applied to alkynyliodide **153** (derived from ethynylglycine synthon **1a**) and carbonyl compound **154** (derived from gluconolactone), leads to propargylic alcohol **155** in 66% yield, as a mixture of diastereoisomers (Fig. 30) (Ayed et al. 2010b).

Unfortunately, when the same alkynyliodide **153** was treated with tri-O-acetyl-D-glucal **156**, no coupling product was detected in the same reaction conditions. Instead of the *C*-glycosylated derivative **157**, the cyclic compound **158** was formed in 91% yield because of Boc intramolecular cyclization (Fig. 30) (Ayed et al. 2010a) (see also the discussion about the amino protecting group issue in our precedent Part I report) (Benfodda et al. 2015).

Indeed, when different protecting groups in alkynyliodide **153** were used (compounds **159** and **161**), the coupling products **160** and **162** (Ferrier-type rearrangement) could be formed exclusively in the α-anomeric form (Fig. 31) (Ayed et al. 2010b, a).

Finally, propargyl hydroxylamine **164** was obtained in 75% yield by a C–C bond-forming reaction using a Lewis acid/metal amide hybrid-catalyzed reaction of ethynylglycine synthon **1a** with nitrone **163** (Fig. 32) (Yamashita et al. 2014).

Miscellaneous

Ethynylglycine synthon **1a** was converted to allenic carbamate **165** using the Crabbé reaction (Fig. 33) (Crabbe et al. 1985; Alcaide et al. 2013).

The 6-methylene 1,3-oxazinan-2-one **166** has then been obtained using a gold-catalyzed oxycyclization of the allene **165** at room temperature (6-*endo-dig* oxyauration, kinetically controlled product). The same reaction conducted at high temperature led to a complex mixture (Fig. 33).

It is worth noting that the same reactions were performed (among other allenic carbamates) on the proline derivative **167**. In that case, the thermodynamically favored 1,3-oxazine-2-one **170** was formed at high temperature (6-*exo-dig* oxyauration) (Fig. 34) (Alcaide et al. 2013).

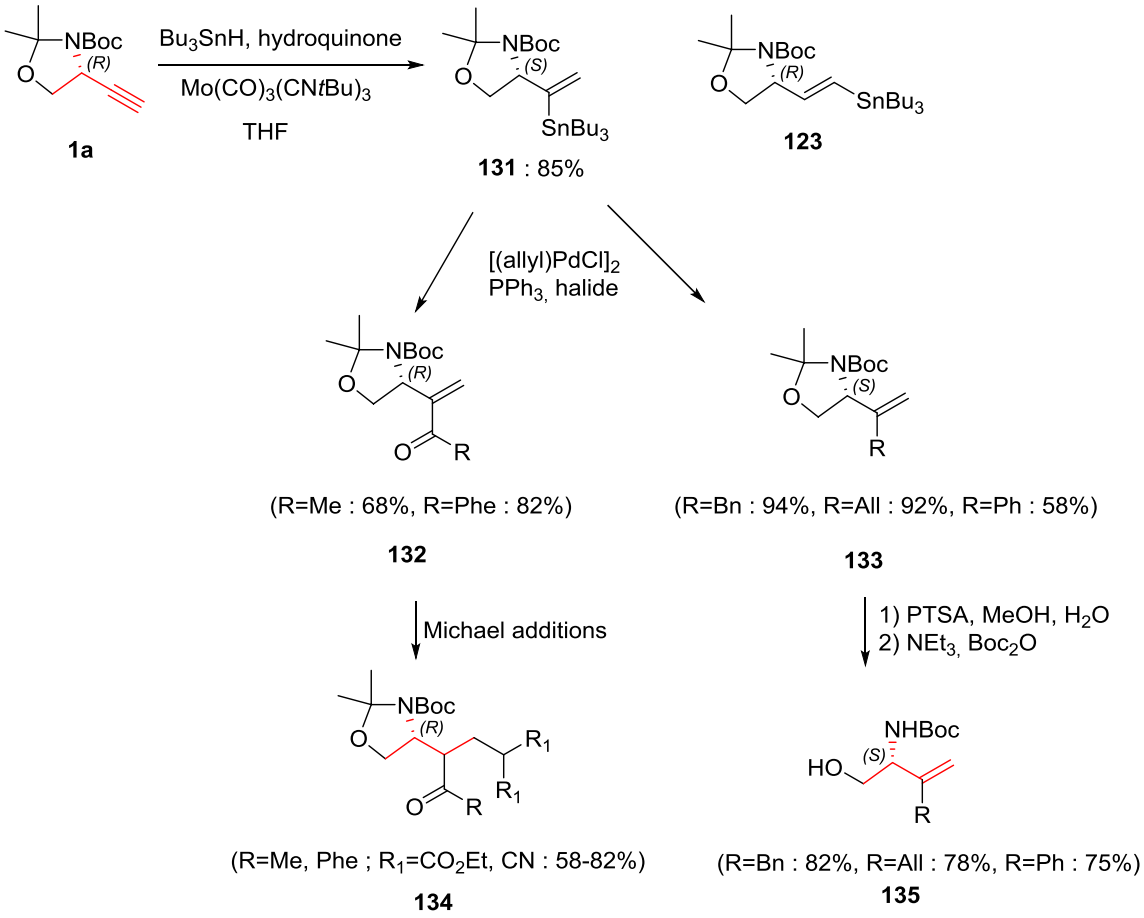


Fig. 27 Synthesis of functionalized amino alcohols and heterocycles by hydrostannation

Ethynylglycine synthon **1a** was converted to protected propargylamine alcohol **171** which was subjected to intramolecular Mitsunobu reaction to lead to aziridine **172**. Bromoallene **174** was then synthesized from aziridine **172** via an acid-mediated ring opening reaction and bromination through mesylate **173** (Fig. 35) (Ohno et al. 2002).

Bromoallene **174** was used as a model in the course of the study of the intramolecular amination reaction of chiral bromoallenes into 2-ethynylaziridines in basic conditions (for example (*R*) and (*S*)-**172** resulted from *syn*- and *anti*-S_N2' processes when bromoallene **174** was treated with LHMDS) (Fig. 35) (Ohno et al. 2002).

To circumvent the Wittig strategy to prepare alkene **175** from Garner's aldehyde **2a** (that proved to be unreliable to some authors) (Belanger et al. 2009), ethynylglycine synthon **1a** was hydrogenated to alkene **175** using Lindlar catalyst. Cross-coupling metathesis using Grubbs' catalyst II led to alkene **177**. This compound is an intermediate in the synthesis of cyclic peptide **178** as a complexing agent of poly(vinyl alcohol) (PVA). This chemistry is outside the scope of this review and will not be detailed here (Fig. 36) (Belanger et al. 2009).

Conclusion

This review shows the great potentiality of ethynylglycine synthon as a polyfunctional chiral building block available for the synthesis of biologically relevant compounds, from "simple" to more "complex" structures. The terminal alkyne moiety has been exploited in metallation and reaction with a large variety of electrophile; in metal-catalyzed coupling reactions (Pd: Sonogashira, Cu, In); in cycloaddition reactions on nitrones, nitrile oxides, azide (Huisgen reaction), Fischer chromium carbene complexes, triazines (hetero-Diels–Alder), and ethyl diazo acetate (Rh-catalyzed cyclopropenation); in additions of stannyl-cuprates followed by Stille coupling reactions. Most of the times, the integrity of the chirality in ethynylglycine synthon was maintained in the final compounds or used as a chiral inducer.

The well-known reactivity of the terminal alkyne together with the presence of the stable chiral aminoalcohol substructure explain the increasing use of the ethynylglycine synthon in recent years (2005–2017: 35 reports) and suggests a great future.

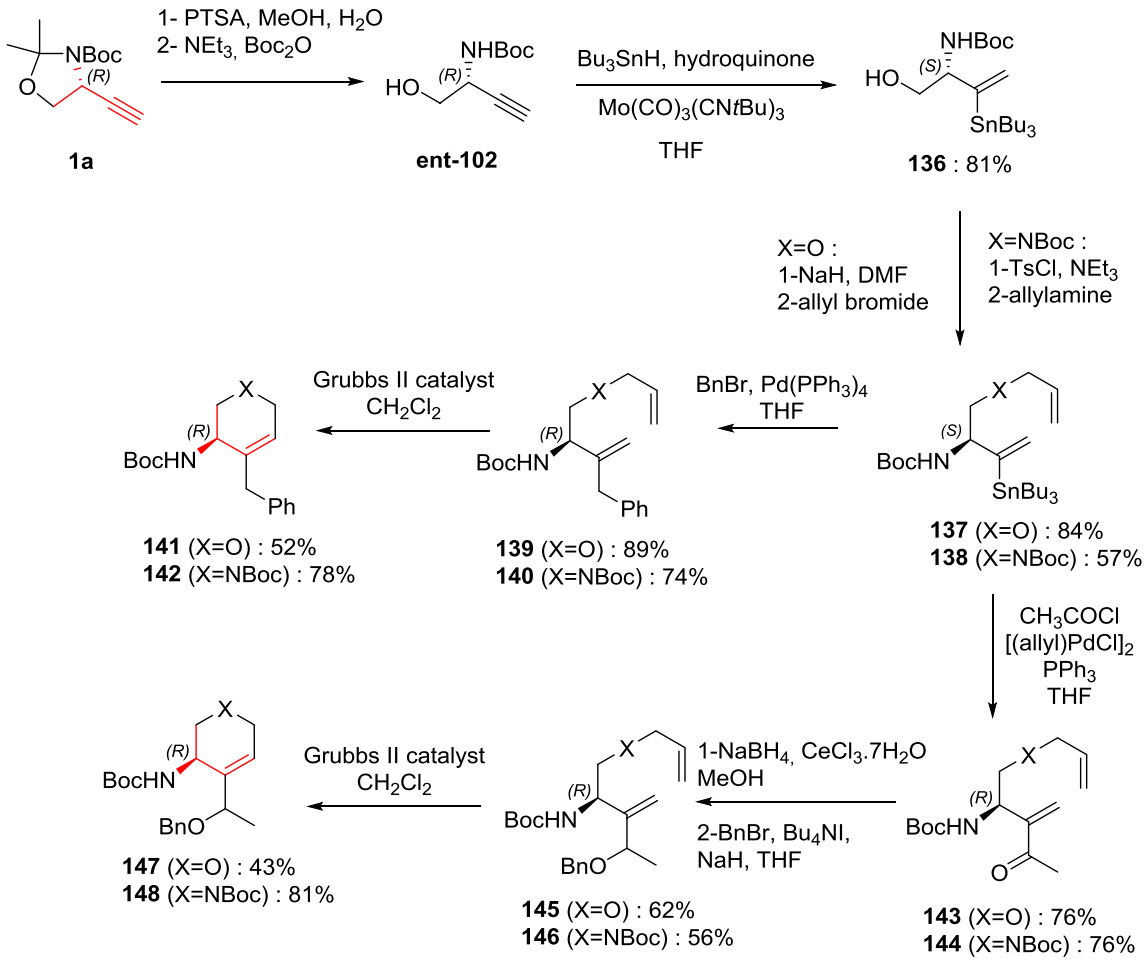


Fig. 28 Synthesis of functionalized amino alcohols and heterocycles by hydrostannation

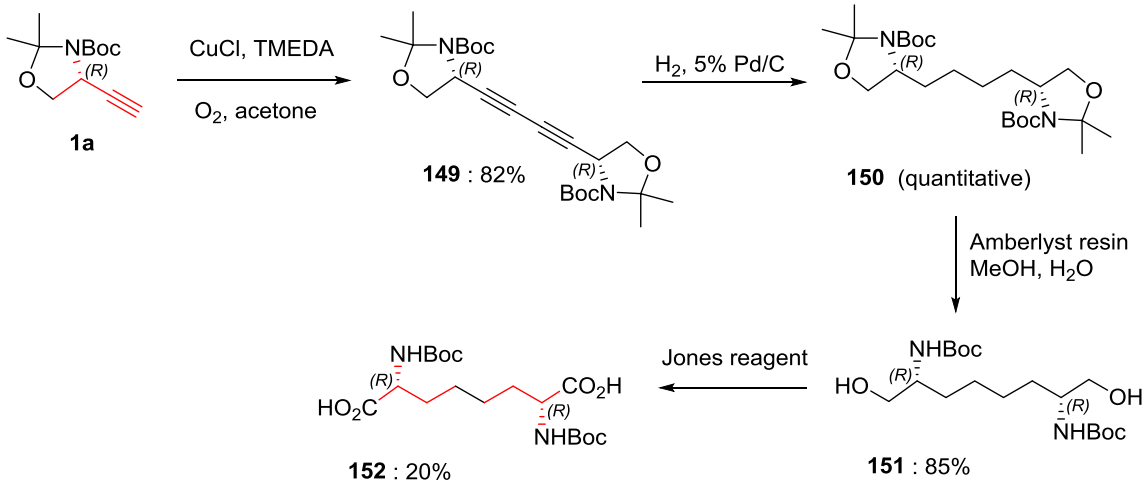


Fig. 29 Synthesis of protected diaminosuberic acid **152**

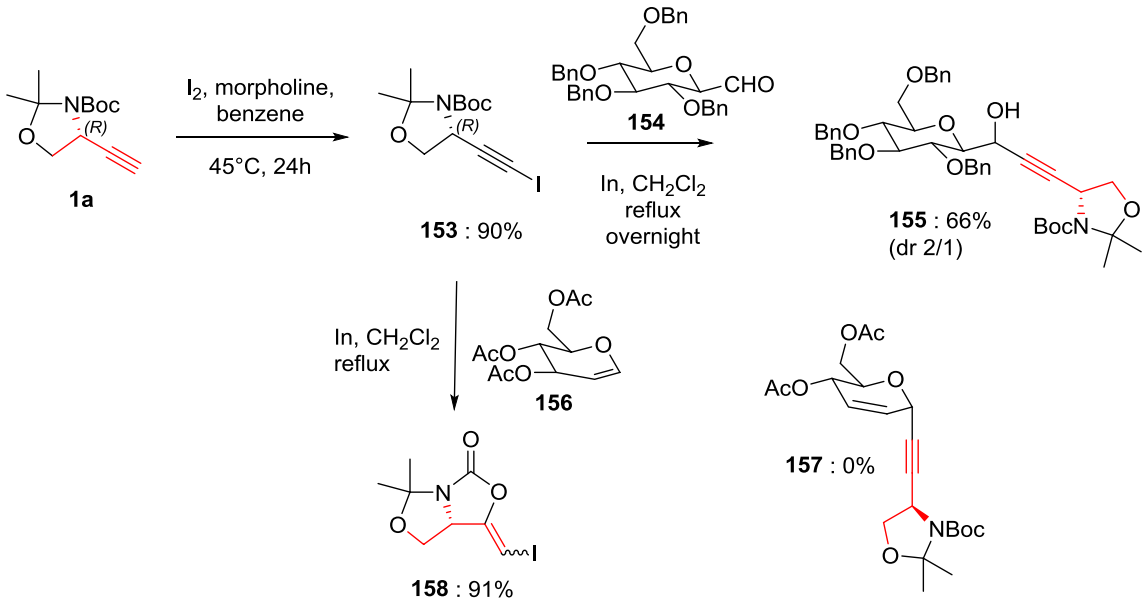


Fig. 30 Synthesis of *C*-glycosylated derivatives and the amino protecting group issue

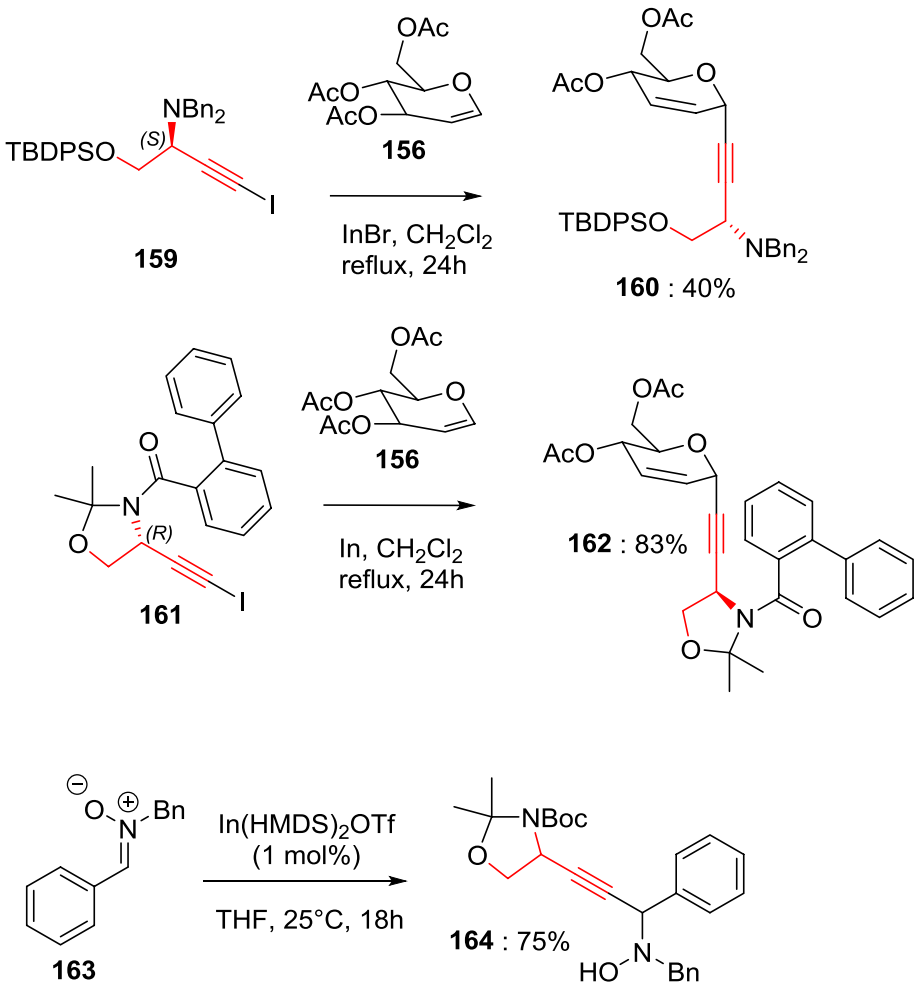


Fig. 32 Synthesis of propargyl hydroxylamine derivative **164**

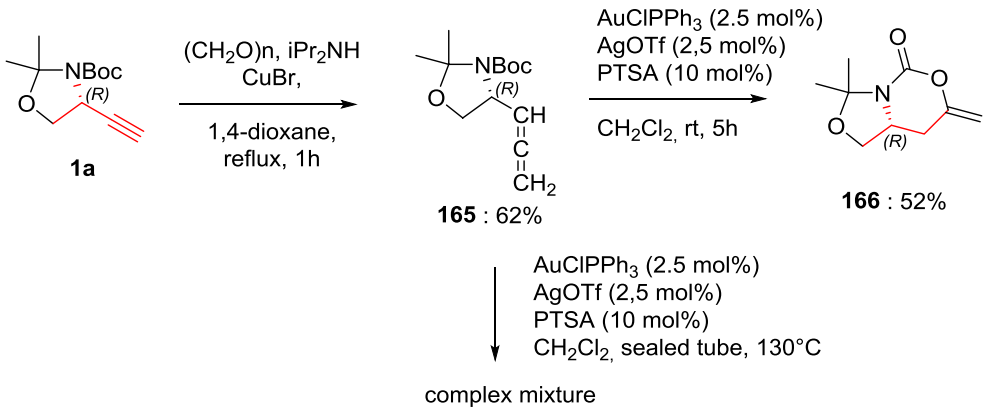


Fig. 33 Synthesis of oxazinone **166**

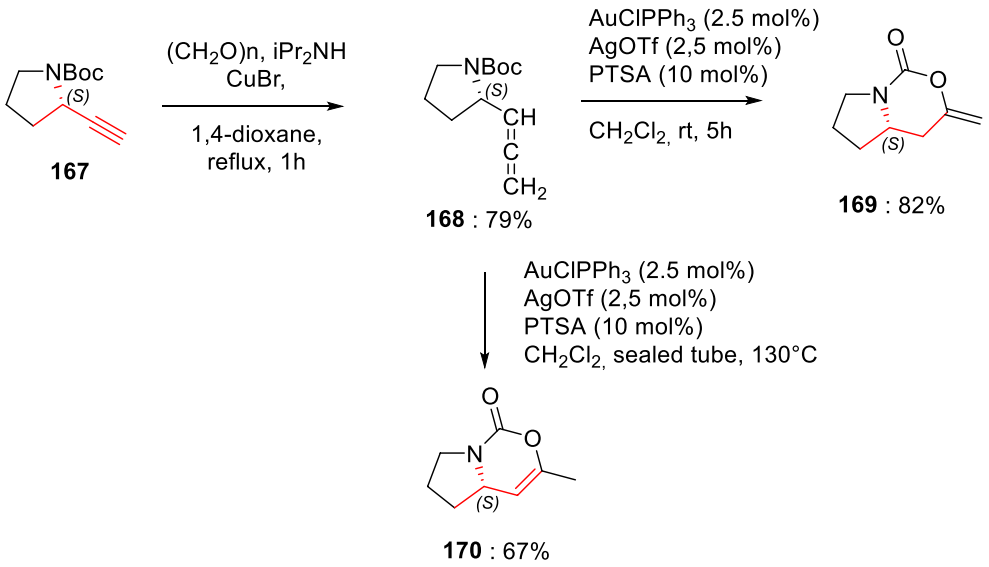


Fig. 34 Synthesis of oxazinones **169** and **170**

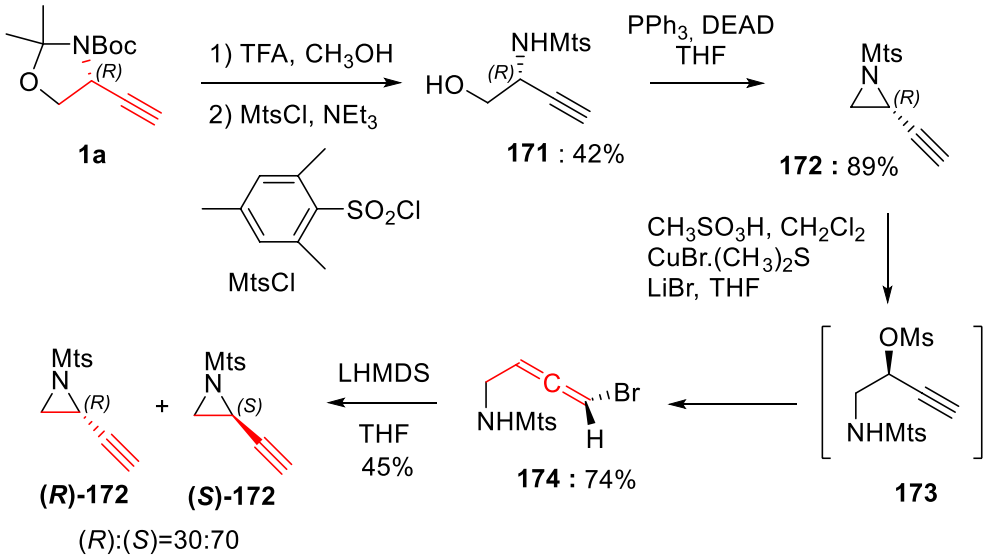


Fig. 35 Synthesis of 2-ethynyl aziridine 172, mixture of enantiomers

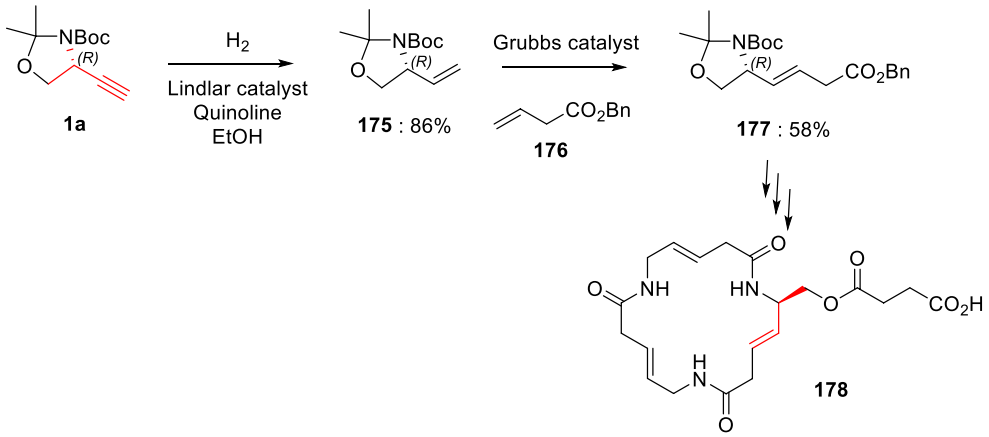


Fig. 36 Synthesis of cyclic peptide **178**

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

Research subjects This review is a compilation of the previous works performed by different authors. No animal or human was used or harmed in this work.

Informed consent This manuscript is being submitted after consent was obtained from all authors, and all authors are aware of this manuscript submission.

References

Alcaide B, Almendros P, Quirós MT, Fernández I (2013) Gold-catalyzed oxycyclization of allenic carbamates: expeditious synthesis of 1,3-oxazin-2-ones. Beilstein J Org Chem 9:818–826. https://doi.org/10.3762/bjoc.9.93

Ayed C, Palmier S, Lubin-Germain N et al (2010a) Indium-mediated alkynylation of sugars: synthesis of *C*-glycosyl compounds bearing a protected amino alcohol moiety. Carbohydr Res 345:2566–2570. https://doi.org/10.1016/j.carres.2010.07.033

Ayed C, Picard J, Lubin-Germain N et al (2010b) Synthesis of alkynes and alkynyl iodides bearing a protected amino alcohol moiety as functionalized amino acids precursors. Sci China Chem 53:1921–1926. https://doi.org/10.1007/s11426-010-4072-2

Badarau E, Suzenet F, Fînaru A-L, Guillaumet G (2009) Synthesis of 3-amino-8-azachromans and 3-amino-7-azabenzofurans via Inverse electron demand Diels–Alder reaction. Eur J Org Chem 2009:3619–3627. https://doi.org/10.1002/ejoc.200900191

Belanger D, Tong X, Soumare S et al (2009) Cyclic peptide-polymer complexes and their self-assembly. Chem Eur J. 15:4428–4436. https://doi.org/10.1002/chem.200802337 **S4428/1-S4428/6**

Benfodda Z, Bénimélis D, Reginato G, Meffre P (2015) Ethynylglycine synthon, a useful precursor for the synthesis of biologically

active compounds: an update. Amino Acids 47:271–279. https://doi.org/10.1007/s00726-014-1902-0
Boibessot T, Bénimèlis D, Jean M et al (2016a) Synthesis of a novel rhizobitoxine-like triazole-containing amino acid. Synlett 27:2685–2688. https://doi.org/10.1055/s-0036-1588300
Boibessot T, Bénimélis D, Meffre P, Benfodda Z (2016b) Advances in the synthesis of α-quaternary α-ethynyl α-amino acids. Amino Acids 48:2081–2101. https://doi.org/10.1007/s00726-016-2276-2
Bolsakova J, Jirgensons A (2016) Synthesis of α-Ethynyl Glycines. Eur J Org Chem 2016:4591–4602. https://doi.org/10.1002/ejoc.201600253
Brummond KM, Yan B (2008) Rhodium(I)-catalyzed cycloisomerization reaction of yne-allenamides: an approach to cyclic enamides. Synlett 2008:2303–2308. https://doi.org/10.1055/s-2008-1078169
Cabarrocas G, Rafel S, Ventura M, Villalgordo J (2000a) A new approach toward the stereoselective synthesis of novel quinolyl glycines: synthesis of the enantiomerically pure Quinolyl-β-amino alcohol precursors. Synlett 2000:0595–0598. https://doi.org/10.1055/s-2000-6625
Cabarrocas G, Ventura M, Maestro M et al (2000b) Reaction between hydrazines and chiral α-acetylenic ketones: synthesis of novel enantiomerically pure pyrazolyl-β-amino alcohols†. Tetrahedron Asymmetry 11:2483–2493. https://doi.org/10.1016/S0957-4166(00)00204-4
Cabarrocas G, Ventura M, Maestro M et al (2001) Synthesis of novel optically pure quinolyl-β-amino alcohol derivatives from 2-amino thiophenol and chiral α-acetylenic ketones and their IBX-mediated oxidative cleavage to N-Boc quinolyl carboxamides. Tetrahedron Asymmetry 12:1851–1863. https://doi.org/10.1016/S0957-4166(01)00308-1
Callahan JF, Khatana SS, Bhatnagar PK (2000) Stereoselective synthesis of diaminosuberic acid via a chiral alkynyl oxazolidine. Synth Commun 30:1213–1219. https://doi.org/10.1080/00397910008087141
Cameron S, Khambay BPS (1998) Stereospecific synthesis of the amino acid, (S)-2-amino-(Z)-3,5-hexadienoic acid. Tetrahedron Lett 39:1987–1990. https://doi.org/10.1016/S0040-4039(98)00112-9
Chinchilla R, Nájera C (2007) The sonogashira reaction: a booming methodology in synthetic organic chemistry. Chem Rev 107:874–922. https://doi.org/10.1021/cr050992x
Chung JYL, Wasicak JT (1990) Synthesis of chiral α-acetylenic cyclic amines from α-amino acids: applications to differentially constrained oxotremorine analogues as muscarinic agents. Tetrahedron Lett 31:3957–3960. https://doi.org/10.1016/S0040-4039(00)94471-X
Comas-Barceló J, Harrity JPA (2017) Metal acetylides in cycloaddition reactions. Synthesis 49:1168–1181. https://doi.org/10.1055/s-0036-1588922
Crabbe P, Schlemper Elmer O, Kay Fair et al (1985) Allene Synthesis by organo-metallic reactions. Isr J Chem 26:147–151. https://doi.org/10.1002/ijch.198500085
Crisp GT, Jiang Y-L, Pullman PJ, De Savi C (1997) Elaboration of the side-chain of amino acid derivatives by palladium catalysed couplings. Tetrahedron 53:17489–17500. https://doi.org/10.1016/S0040-4020(97)10197-1
Dondoni A, Mariotti G, Marra A, Massi A (2001) Expeditious synthesis of β-linked glycosyl serine methylene isosteres (β-*C*-glyser) via ethynylation of sugar lactones. Synthesis. https://doi.org/10.1055/s-2001-18058
Erdsack J, Krause N (2007) Synthesis of furanomycin derivatives by gold-catalyzed cycloisomerization of α-hydroxyallenes. Synthesis 2007:3741–3750. https://doi.org/10.1055/s-2007-990860
Evidente A, Kornienko A, Cimmino A et al (2014) Fungal metabolites with anticancer activity. Nat Prod Rep 31:617–627. https://doi.org/10.1039/C3NP70078J
Falorni M, Giacomelli G, Spanu E (1998) Synthesis of new α-amino-acids containing the isoxazole moiety. Tetrahedron Lett 39:9241–9244. https://doi.org/10.1016/S0040-4039(98)02010-3
Frydenvang K, Pickering DS, Greenwood JR et al (2010) Biostructural and pharmacological studies of bicyclic analogues of the 3-isoxazolol glutamate receptor agonist ibotenic acid. J Med Chem 53:8354–8361. https://doi.org/10.1021/jm101218a
Giacomelli G, De Luca L, Porcheddu A (2003) A method for generating nitrile oxides from nitroalkanes: a microwave assisted route for isoxazoles. Tetrahedron 59:5437–5440. https://doi.org/10.1016/S0040-4020(03)00859-7
Goswami K, Duttagupta I, Sinha S (2012a) Synthesis of optically active 2- and 3- indolylglycine derivatives and their oxygen analogues. J Org Chem 77:7081–7085. https://doi.org/10.1021/jo300708h
Goswami K, Paul S, Bugde ST, Sinha S (2012b) Synthesis of optically active homotryptophan and its oxygen and sulfur analogues. Tetrahedron 68:280–286. https://doi.org/10.1016/j.tet.2011.10.055
Goswami K, Chakraborty A, Sinha S (2013) Synthesis of optically active selenium-containing isotryptophan, homoiso-tryptophan, and homotryptophan. Eur J Org Chem 2013:3645–3647. https://doi.org/10.1002/ejoc.201300352
Govek SP, Overman LE (2007) Total synthesis of (+)-asperazine. Tetrahedron 63:8499–8513. https://doi.org/10.1016/j.tet.2007.05.127
Guillarme S, Plé K, Haudrechy A (2006) Selective synthesis of α-*C*-(Alkynyl)-galactosides by an efficient tandem reaction. J Org Chem 71:1015–1017. https://doi.org/10.1021/jo0519817
Holmberg P, Sohn D, Leideborg R et al (2004) Novel 2-aminotetralin and 3-aminochroman derivatives as selective serotonin 5-HT7 receptor agonists and antagonists. J Med Chem 47:3927–3930. https://doi.org/10.1021/jm0498102
Holmberg P, Tedenborg L, Rosqvist S, Johansson AM (2005) Novel 3-aminochromans as potential pharmacological tools for the serotonin 5-HT7 receptor. Bioorg Med Chem Lett 15:747–750. https://doi.org/10.1016/j.bmcl.2004.11.013
Huisgen R (1963) 1,3-Dipolar Cycloadditions. Past and Future. Angew Chem Int Ed Engl 2:565–598. https://doi.org/10.1002/anie.196305651
Katagiri K, Tori K, Kimura Y et al (1967) A new antibiotic. furanomycin, an isoleucine antagonist. J Med Chem 10:1149–1154. https://doi.org/10.1021/jm00318a035
Kavitha M, Mahipal B, Mainkar PS, Chandrasekhar S (2011) Click reaction on in situ generated β-azidostyrenes from cinnamic acid using CAN–NaN3: synthesis of *N*-styryl triazoles. Tetrahedron Lett 52:1658–1662. https://doi.org/10.1016/j.tetlet.2011.01.129
Khutorianskyi A, Chalyk B, Borysko P et al (2017) Difluoromethyl nitrile oxide (CF2HCNO): a neglected chemical reagent. Eur J Org Chem 2017:3935–3940. https://doi.org/10.1002/ejoc.201700764
Kumar P, Shukhman D, Laughlin ST (2016) A photocaged, cyclopropene-containing analog of the amino acid neurotransmitter glutamate. Tetrahedron Lett 57:5750–5752. https://doi.org/10.1016/j.tetlet.2016.10.106
Lin H, Kazmaier U (2007) Regioselective mo-catalyzed hydrostannations as key steps in the synthesis of functionalized amino alcohols and heterocycles. Eur J Org Chem 2007:2839–2843. https://doi.org/10.1002/ejoc.200700126
Mallampudi NA, Reddy GS, Maity S, Mohapatra DK (2017) Gold(I)-Catalyzed Cyclization for the Synthesis of 8-Hydroxy-3—substituted Isocoumarins: total Synthesis of Exserolide F. Org Lett 19:2074–2077. https://doi.org/10.1021/acs.orglett.7b00673
Mazuela J, Antonsson T, Johansson MJ et al (2017) Direct Synthesis of N-Alkyl Arylglycines by Organocatalytic Asymmetric Transfer

Hydrogenation of N-Alkyl Aryl Imino Esters. Org Lett. https://doi.org/10.1021/acs.orglett.7b02627
Meffre P, Le Goffic F (1996) β, γ-Alkynylα-amino acids: a synthetic challenge. Amino Acids 11:313–328. https://doi.org/10.1007/BF00807939
Meffre P, Gauzy L, Branquet E et al (1996) Synthesis of optically active β, γ-alkynylglycine derivatives. Tetrahedron 52:11215–11238. https://doi.org/10.1016/0040-4020(96)00630-8
Ohno H, Ando K, Hamaguchi H et al (2002) A highly cis-selective synthesis of 2-ethynylaziridines by intramolecular amination of chiral bromoallenes: improvement of stereoselectivity based on the computational investigation. J Am Chem Soc 124:15255–15266. https://doi.org/10.1021/ja0262277
Owens LD, Guggenheim S, Hilton JL (1968) Rhizobium-synthesized phytotoxin: an inhibitor of β-cystathionase in Salmonella typhimurium. Biochim Biophys Acta BBA Gen Subj 158:219–225. https://doi.org/10.1016/0304-4165(68)90134-7
Pulley SR, Sen S, Vorogushin A, Swanson E (1999) Diaryl ethers using fischer chromium carbene mediated benzannulation. Org Lett 1:1721–1723. https://doi.org/10.1021/ol990949u
Pulley SR, Czakó B, Brown GD (2005) Synthesis of arylglycines via the Dötz benzannulation reaction. Tetrahedron Lett 46:9039–9042. https://doi.org/10.1016/j.tetlet.2005.10.105
Raji Reddy C, Krishna G, Kavitha N et al (2012) Access to 2,3-disubstituted benzofurans through one-pot acid-catalyzed nucleophilic substitution/TBAF-mediated oxacycloisomerization. Eur J Org Chem 2012:5381–5388. https://doi.org/10.1002/ejoc.201200708
Reginato G, Mordini A, Degl'Innocenti A, Caracciolo M (1995) Stereoselective synthesis of (R)-(−)-2,2-dimethyl-3-t-butoxycarbonyl-4-ethynyl-oxazolidine: a chiral building block for the synthesis of a new class of substituted alkynes. Tetrahedron Lett 36:8275–8278. https://doi.org/10.1016/0040-4039(95)01725-w
Reginato G, Mordini A, Caracciolo M (1997) Synthetic Elaboration of the Side Chain of (R)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine: a new regio—and stereoselective strategy to δ-functionalized β-amino alcohols. J Org Chem 62:6187–6192. https://doi.org/10.1021/jo970619s
Reginato G, Mordini A, Valacchi M (1998) A stereoselective approach to the synthesis of γ-silylated amino acids. Tetrahedron Lett 39:9545–9548. https://doi.org/10.1016/S0040-4039(98)02120-0
Reginato G, Mordini A, Valacchi M, Grandini E (1999) Silylcupration of (*R*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine: a stereoselective approach to the synthesis of γ-silylated saturated and unsaturated α-amino acids. J Org Chem 64:9211–9216. https://doi.org/10.1021/jo991272r
Reginato G, Mordini A, Verrucci M et al (2000) A new approach to non racemic saturated and unsaturated 5-aminoalkyl methyl ketones. Tetrahedron Asymmetry 11:3759–3768. https://doi.org/10.1016/S0957-4166(00)00335-9
Reginato G, Gaggini F, Mordini A, Valacchi M (2005a) Stereoselective synthesis of dienylamines: from amino acids to E-alkene dipeptide isosters. Tetrahedron 61:6791–6800. https://doi.org/10.1016/j.tet.2005.04.068
Reginato G, Meffre P, Gaggini F (2005b) Ethynylglycine synthon from Garner's aldehyde: a useful precursor for the synthesis of non-natural amino acids. Amino Acids 29:81–87. https://doi.org/10.1007/s00726-005-0184-y
Reginato G, Mordini A, Meffre P et al (2006) New unsaturated amino acids containing an allylsilane moiety on the lateral chain. Tetrahedron Asymmetry 17:922–926. https://doi.org/10.1016/j.tetasy.2006.02.017
Röhrig UF, Awad L, Grosdidier A et al (2010) Rational design of indoleamine 2,3-dioxygenase inhibitors. J Med Chem 53:1172–1189. https://doi.org/10.1021/jm9014718
Serrat X, Cabarrocas G, Rafel S et al (1999) A highly efficient and straightforward stereoselective synthesis of novel chiral α-acetylenic ketones. Tetrahedron Asymmetry 10:3417–3430. https://doi.org/10.1016/S0957-4166(99)00357-2
Spangenberg T, Schoenfelder A, Breit B, Mann A (2010) 1,2-Diastereoselective C–C bond-forming reactions for the synthesis of chiral β-branched α-amino acids. Eur J Org Chem 2010:6005–6018. https://doi.org/10.1002/ejoc.201000865
Stecko S, Mames A, Furman B, Chmielewski M (2009) Asymmetric kinugasa reaction of cyclic nitrones and nonracemic acetylenes. J Org Chem 74:3094–3100. https://doi.org/10.1021/jo900121x
Sugawara M, Okazaki S, Nukui N et al (2006) Rhizobitoxine modulates plant–microbe interactions by ethylene inhibition. Biotechnol Adv 24:382–388. https://doi.org/10.1016/j.biotechadv.2006.01.004
Totobenazara J, Burke AJ (2015) New click-chemistry methods for 1,2,3-triazoles synthesis: recent advances and applications. Tetrahedron Lett 56:2853–2859. https://doi.org/10.1016/j.tetlet.2015.03.136
Usuki T, Yamada H, Hayashi T et al (2012) Total synthesis of COPD biomarker desmosine that crosslinks elastin. Chem Commun 48:3233–3235. https://doi.org/10.1039/C2CC17958J
von Nussbaum F, Brands M, Hinzen B et al (2006) Antibacterial Natural Products in Medicinal Chemistry—Exodus or Revival? Angew Chem Int Ed 45:5072–5129. https://doi.org/10.1002/anie.200600350
Wzorek JS, Knöpfel TF, Sapountzis I, Evans DA (2012) A macrocyclic approach to tetracycline natural products. investigation of transannular alkylations and michael additions. Org Lett 14:5840–5843. https://doi.org/10.1021/ol302691j
Xiong K, Fuhrmann JJ (1996) Comparison of rhizobitoxine-induced inhibition of β-cystathionase from different bradyrhizobia and soybean genotypes. Plant Soil 186:53–61. https://doi.org/10.1007/BF00035055
Yamada H, Hayashi T, Usuki T (2015) Total synthesis of the COPD biomarker desmosine via stepwise sonogashira Cross-coupling reactions. Bull Chem Soc Jpn 88:673–683. https://doi.org/10.1246/bcsj.20140394
Yamakawa T, Ideue E, Shimokawa J, Fukuyama T (2010) Total synthesis of tryprostatins A and B. Angew Chem Int Ed 49:9262–9265. https://doi.org/10.1002/anie.201004963
Yamakawa T, Ideue E, Iwaki Y et al (2011) Total synthesis of tryprostatin A and B. Tetrahedron 67:6547–6560. https://doi.org/10.1016/j.tet.2011.05.112
Yamakawa T, Ideue E, Shimokawa J, Fukuyama T (2014) Corrigendum: total synthesis of tryprostatins A and B. Angew Chem Int Ed 53:8808–8808. https://doi.org/10.1002/anie.201401055
Yamashita Y, Saito Y, Imaizumi T, Kobayashi S (2014) A Lewis acid/metal amide hybrid as an efficient catalyst for carbon-carbon bond formation. Chem Sci 5:3958–3962. https://doi.org/10.1039/C4SC01332H
Yanada R, Obika S, Kobayashi Y et al (2005) Stereoselective synthesis of 3-alkylideneoxindoles using tandem indium-mediated carbometallation and palladium-catalyzed cross-coupling reactions. Adv Synth Catal 347:1632–1642. https://doi.org/10.1002/adsc.200505147
Yasuta T, Satoh S, Minamisawa K (1999) New assay for rhizobitoxine based on inhibition of 1-aminocyclopropane-1-carboxylate synthase. Appl Environ Microbiol 65:849–852