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Stereoselective synthesis of new enantiomerically enriched N-protected γ-amino acetylenic esters.

Gianna Reginato*[a], Alessandro Mordini[a], Antonella Capperucci[b], Alessandro Degl'Innocenti[b], Sonia Manganiello[b]

a) *CNR-Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni*

b) *Dipartimento di Chimica Organica "U. Schiff" via G. Capponi 9, I-50121 Firenze- Italy*

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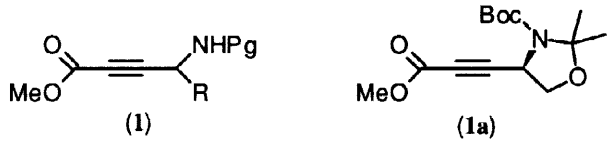
Abstract : A new class of differently protected chiral γ-amino acetylenic esters have been synthesized using natural occurring amino acids as chiral source. Enantiomerically enriched propargylamines or vinyldibromides have been treated with BuLi at low temperature affording, after carboxylation, enantiomerically enriched derivatives of alkynologous amino esters.

Keywords: Alkynes; Amino acids and derivatives; Amino aldehydes; Carboxylation.

1. Introduction

γ-Amino acetylenic esters (**1**) are interesting substrates as precursors of nitrogen containing heterocycles [1][2][3], as for example substituted pyrrolin-2-ones or substituted pyrrole derivatives. Despite this interest, a few methods for their synthesis [1][4] have been developed, especially in the chiral series.



(1) (1a)

Scheme 1

* Corresponding author: E-mail: reginato@chimorg.unifi.it

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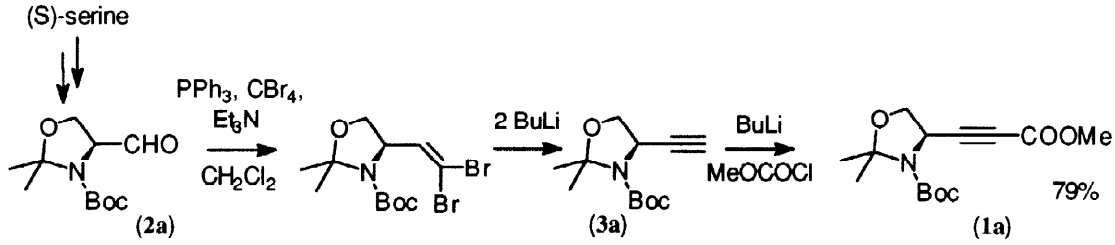
We have recently found that oxazolidine (**1a**) can be obtained with high enantiomeric purity using Boc-protected naturally occurring (*L*)-serine as starting material [5][6] and we have shown that it is a suitable precursor of the corresponding amino alcohol. Our strategy was based on the Corey-Fuchs [7] transformation of the Garner [8] aldehyde (**2a**) to the corresponding alkyne (**3a**) which, after treatment with BuLi and carboxylation with methyl chloroformate, afforded compound (**1a**) without racemization and in a very good yield (Scheme 2). Later on, a very similar procedure has been applied to the synthesis of optically pure alkynologous amino acids [9], a series of compounds that are expected to be of interest in planning new peptido-mimetic drugs.



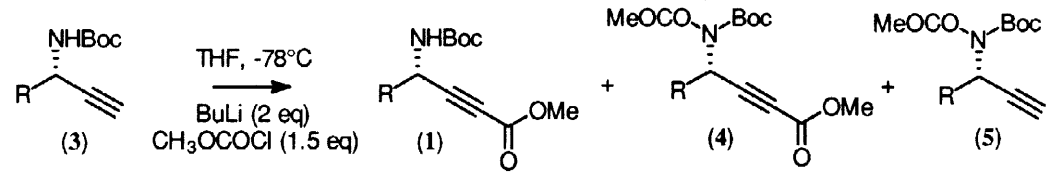
Scheme 2

In order to check the potentialities of the above mentioned procedure we too have extended this reaction sequence to a series of chiral propargylamines (**3**). We report here the results of such investigation, which highlight the crucial role of the protective group in determining the efficiency of the whole process as a general method for the synthesis of N-protected γ-amino acetylenic esters (**1**).

2. Results and discussion

When amine (**3b**) [10] was treated with BuLi (1eq) at low temperature and reacted with excess CH_3OCOCl, ester (**1b**) was recovered in a good yield after basic aqueous work up.

Unfortunately this procedure didn't prove to be general. Reaction of amine (**3c**) for example afforded, together with (**1c**), sizeable amounts of by-products (**4c**) and (**5c**) derived from carboxylation at nitrogen. This side reaction represent a serious drawback and became predominant in case of amine (**3d**), thus preventing recovery of ester (**1d**) (see Scheme 3). Treatment of the starting propargylamines with different bases such as NaHMDS or MeMgBr failed to provide the desired compound.

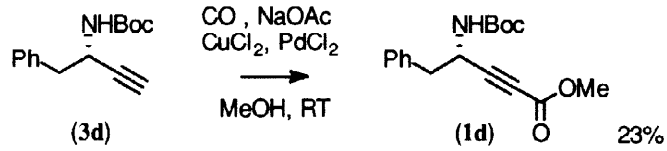


Starting amino acid	Alkyne	Conversion[a]		
	(3)	(1)[b]	(4)	(5)
Valine (R=CH(CH$_3$)$_2$)	(3b)	(1b) 85% (60%)	(4b) 5%	(5b) -
Isoleucine (R=CH(CH$_3$)CH$_2$CH$_3$)	(3c)	(1c) 30% (26%)	(4c) 30%	(5c) 15%
Phenylalanine (R=CH$_2$Ph)	(3d)	(1d) -	(4d) 25%	(5d) 40%

(a) Determined by ^{1}H NMR analysis of the crude mixture
(b) Yields in parentheses are of isolated compound

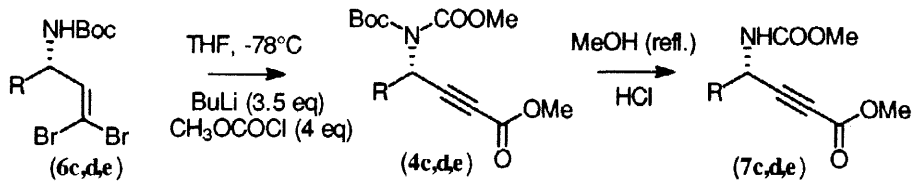
Scheme 3

In order to obtain (**1d**), we tried a different and milder procedure. It is known [11] that carboxylation of terminal alkynes can be achieved by treatment with copper(II) chloride and sodium acetate in methanol under an atmosphere of carbon monoxide and in the presence of a catalytic amount of palladium(II) chloride. This procedure has been successfully applied to chiral substrates but no data are available with propargylamines. Our attempts to perform the reaction on compound (**3d**) resulted in a complex mixture of by-products from which compound (**1d**) was indeed isolated after purification but in a very low yield.



Scheme 4

Alternatively we decided to slightly modify our target. Direct treatment of the vinylbromide (**6d**) with BuLi (3.5 eq) at low temperature followed by reaction with excess MeOCOCl (4 eq) allowed a one step and high yielding transformation into the ester (**4d**). After reflux of the crude mixture with acidic methanol only the *t*-Boc protecting group was removed and the corresponding methoxycarbonyl derivative (**7d**) was obtained after purification by flash chromatography. The extension of this reaction sequence to different substrates (**6c, 6e**) gave an analogous result, as shown in Scheme 5.

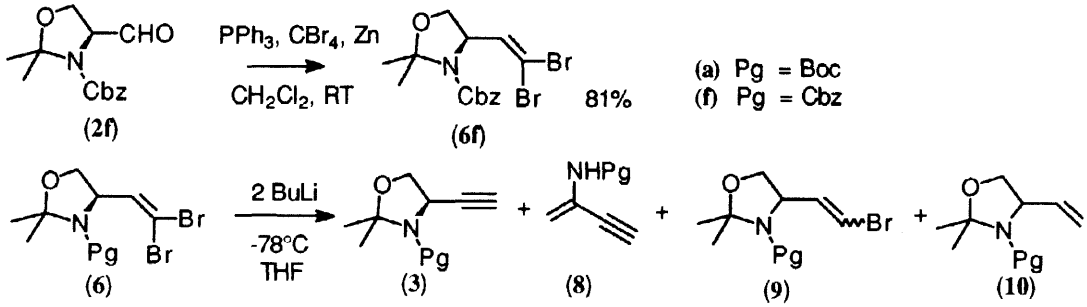


Starting amino acid	Yield	
Isoleucine (R=CH(CH$_3$)CH$_2$CH$_3$)	(4c) 68% [a]	(7c) > 95% (37%)[b]
Phenylalanine (R=CH$_2$Ph)	(4d) 90%[a]	(7d) > 95% (46%)[b]
Leucine (R=CH(CH$_3$)$_2$)	(4e) 85%[a]	(7e) > 95% (39%)[b]

(a) Not isolated
(b) Yields in parentheses are of isolated compound, calculated from the starting bromide.

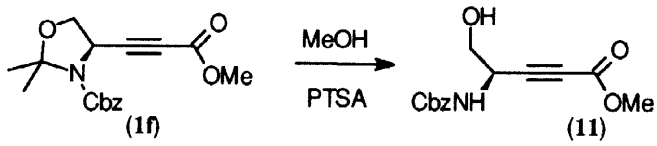
Scheme 5

Finally we checked our reaction sequence on a differently protected oxazolidine derivative. The benzyloxycarbonyl protected aldehyde [12] (**2f**) was chosen as starting material and easily transformed into the corresponding dibromide (**6f**). Surprisingly the subsequent transformation to the terminal triple bond was shown to be less efficient compared with our previous results [5][6]. Treatment of (**6f**) with BuLi at low temperature gave an inseparable mixture of compounds (**3f**), (**9f**) and (**10f**), in which (**3f**) was predominant. In our opinion a reason for this behavior could be ascribed to a different participation of the Boc neighboring protective group in assisting the metalation of the vinylic proton [13][14]. This hypothesis is also in agreement with the fact that, while the synthesis of compound (**3a**) from (**6a**) was always accompanied with the formation of variable amounts of (**8a**) [6], in the case of substrate (**6f**) enamine (**8f**) was never recovered in the reaction mixture, even if an excess of BuLi was used for a prolonged reaction time.



Scheme 6

Esterification of the Cbz protected ethynyloxazolidine was therefore performed directly by treatment of the crude mixture with BuLi at low temperature and then with MeOCOCl in excess. Product (**1f**) was obtained in this way in 41% overall yield (from **6f**) after purification.



Scheme 7

Deprotection in refluxing wet MeOH with PTSA, afforded pure (**11**) in 90% yield. The enantiomeric purity of compound (**11**) was then established by ^{1}H-NMR analysis of the diastereomeric Mosher esters obtained by reaction with both (*R*)-(-), and (*S*)-(+)-MTPACl[15]. The two diastereomers were found to be clearly distinguishable and showed no contamination from racemized material.

In conclusion, we can say that the Corey-Fuchs transformation of chiral aldehydes derived from natural amino acids has been shown to be an efficient procedure for the stereoselective synthesis of γ-amino acetylenic esters, but an optimization of the reaction conditions is required depending on different substrates.

3. Experimental

General methods. All reactions were carried out under dry nitrogen. Ethereal extracts were dried with Na_2SO_4. Reactions were monitored by TLC on SiO_2, detection was made using a basic $KMnO_4$ solution. Flash column chromatography[16] was performed using glass columns (10-50 mm wide) and SiO_2 (230-400 mesh). ^{1}H-NMR spectra were recorded at 200 or 300 MHz. ^{13}C-NMR spectra were recorded at 50.3 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: δ 7.26 ppm ^{1}H; $CHCl_3$: δ 77.0 ppm ^{13}C). ^{19}F-NMR spectra were recorded at 282.2 MHz. C_6F_6 (δ −163.0 ppm) was used as internal standard. Coupling constants (*J*) are reported in Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of a doublet), m (multiplet), bs (broad singlet). Mass spectra were obtained at 70 eV ionization potential and are reported in the form *m/z* (intensity relative to base = 100). Polarimetric measurements were performed in $CHCl_3$ solution at λ = 589 nm, and the temperature is specified case by case. IR spectra were recorded in CCl_4 solution.

Materials. Propargylic amines (**3b,c,d**), vinyldibromides (**6c,d,e**) and 2,2-dimethyl-3-(benzyloxycarbonyl)-4-oxo-oxazolidine (**2f**) were prepared according to the literature[10][12].

Starting materials are commercially available unless otherwise stated. All commercial reagents were used without further purification. THF was dried by distillation over sodium benzophenone ketyl. Petroleum ether, unless specified, is the 40-70°C boiling fraction.

General procedure for the synthesis of alkynoates (**1**).

A solution of (**3**) in THF was cooled at -78 °C and reacted with BuLi (2 eq). The mixture was stirred for 15 min. Methyl chloroformate was added and the reaction mixture was left at -78 °C for 30 min, diluted with ether and hydrolyzed with aqueous NaOH (0.01 M). The organic phase was separated and washed with brine, dried, evaporated and purified by flash chromatography.

(S)-Methyl 4-(tert-butoxycarbonylamino)-5-methyl-2-hexynoate (**1b**). A solution of (**3b**), 127 mg (0.6 mmol), in THF (5 mL) was reacted with 0.8 mL (1.3 mmol) of BuLi and with 90 mg (0.9 mmol) of CH_3OCOCl. After work-up and purification (eluent: petroleum ether/ethyl acetate 7/1) 98 mg (60%) of pure (**1b**) was obtained as a white solid.

(**1b**): m.p. 95-98 °C. ^{1}H-NMR (200 MHz) δ 4.84 [bd, 1H, *J* = 7.0 Hz, NH]; 4.50-4.39 [m, 1H, CH-N]; 3.73 [s, 3H, OCH_3]; 2.02-1.81 [m,1H, CH], 1.41 [s, 9H, 3xCH_3]; 0.97 [d, 6H, *J* = 7.0 Hz, 2xCH_3]. ^{13}C-NMR (50.3 MHz) δ 154.7; 153.6; 86.2; 80.1; 75.2; 52.6; 48.4; 33.0; 28.2; 18.5; 17.8. MS *m/z*: 212(11); 57(100). $[\alpha]^{19}_D$ = -76.7 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}): 1772. Anal. Calcd. for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.34; H, 8.32; N, 5.47.

(4S,5S)-Methyl 4-(tert-butoxycarbonylamino)-5-methyl-2-heptynoate (**1c**). A solution of (**3c**) (426 mg, 2.0 mmol) in THF (10 mL) was reacted with BuLi (2.5 mL, 4.0 mmol) and with 236 mg (2.5 mmol) of CH_3OCOCl. Work-up and purification (eluent: petroleum ether/ethyl acetate = 7/1) afforded 140 mg (26%) of pure (**1c**) as a white solid.

(**1c**): m.p.112-115 °C. ^{1}H-NMR (300 MHz) δ 4.90 [bd, 1H, *J* = 8.4 Hz, NH]; 4.59-4.44 [m, 1H, CH-N]; 3.71 [s, 3H, CH_3]; 1.72-1.49 [m, 1H, CH], 1.49-1.41 [m, 1H, CH_2], 1.39 [s, 9H, 3xCH_3]; 1.31-1.10 [m, 1H, CH_2], 0.93 [d, 3H, *J* = 6.8 Hz, CH_3], 0.87 [t, 3H, *J* = 7.2 Hz, CH_3]. ^{13}C-NMR (50.3 MHz) δ: 154.6; 153.6; 86.0; 80.0; 75.4; 52.5; 47.2; 39.2; 28.1; 25.7; 14.5; 11.2. MS *m/z* 212(5); 182(4); 157(6); 125(26); 112(45); 97(13); 85(17); 71(21); 59(13); 57(100). $[\alpha]^{19}_D$ =-64.8 (*c* = 1.0, $CHCl_3$). Anal. Calcd. for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.34; H, 8.62; N, 5.17.

Synthesis of (S)-Methyl 4-(tert-butoxycarbonylamino)-5-phenyl-2-pentynoate (**1d**). A solution of (**3d**) (268 mg, 1.1 mmol) in degassed MeOH (40 mL), was treated with 180 mg (2.2 mmol) of NaOAc, 296 mg (2.2 mmol) of $CuCl_2$, 12 mg (5%) of $PdCl_2$ and maintained under 1 atm. of CO gas for 4 h at r.t., until the solution turned from green to black. The solvent was evaporated, the residue dissolved with ether and the solution filtered on SiO_2. The organic layer was washed with

$NaHCO_3$ solution, dried and evaporated. Purification of the crude mixture (279 mg) (eluent: petroleum ether/ethyl acetate = 5/1) afforded 76 mg (23%) of (**1d**).

(**1d**): ^{1}H-NMR (200 MHz) δ: 7.39-7.21 [m, 5H, 5xCH ar]; 4.81 [bs, 1H+1H, NH+CH]; 3.75 [s, 3H, CH_3]; 3.05-2.94 [m, 2H, CH_2]; 1.42 [s, 9H, 3xCH_3]. ^{13}C-NMR (50.3 MHz) δ: 154.3; 153.6; 135.4; 129.6; 128.5; 127.2; 86.4; 80.4; 75.4; 52.7; 43.7; 41.1; 28.2. MS *m/z*: 248(20); 230(6); 216(10); 203(13); 171(16); 144(27); 112(55); 91(54); 90(64); 57(100). $[\alpha]^{20}_D$ = - 36.7 (*c* = 0.95, $CHCl_3$). IR (cm^{-1}): 1721.

General procedure for the synthesis of alkynoates (**7**).

A solution of (**6**) in THF was cooled at -78 °C and reacted with BuLi (3.5 eq). The mixture was stirred for 15 min, CH_3OCOCl (4 eq) was then added and the reaction mixture left at -78 °C for 4 h, then diluted with ether and with aqueous NaOH (0.01 M). The organic phase was separated, washed with brine, dried and evaporated. ^{1}H-NMR analysis showed the presence of compound (**4**). Refluxing of the crude mixture in acidic MeOH afforded pure compound (**7**) after flash chromatography.

(4S,5S)-Methyl 4-(methoxycarbonylamino)-5-methyl-2-heptynoate (**7c**). A solution of (**6c**) (550 mg, 1.5 mmol) in THF (5mL) was reacted with BuLi (3.3 mL, 5.2 mmol) and with 586 mg (6 mmol) of CH_3OCOCl. After work-up 315 mg of crude (**4c**) was obtained.

(**4c**): ^{1}H-NMR (200 MHz) δ: 4.87 [d, 1H, *J*=10.4 Hz, CH-N]; 3.78[s, 3H, OCH_3]; 3.69 [s, 3H, OCH_3]; 2.21-2.05 [m, 1H, CH]; 1.46 [s, 9H, 3xCH_3]; 1.03-0.89 [m, 2H+3H, CH_2+CH_3], 0.80 [t, 3H, *J*=7.2 Hz, CH_3].

The crude product (315 mg) was refluxed in MeOH/HCl for 2 h. Evaporation of the solvent and purification (eluent: petroleum ether/ethyl acetate 5/1) afforded 127 mg (37%) of pure (**7c**).

(**7c**): ^{1}H-NMR (200 MHz) δ: 5.10-4.98 [m, 1H, NH]; 4.64-4.54 [m, 1H, CH-N]; 3.75 [s, 3H, OCH_3]; 3.67 [s, 3H, OCH_3]; 1.74-1.41 [m, 1H+1H, CH+CH_2]; 1.34-1.15 [m, 1H, CH_2]; 0.99-0.88 [m, 3H+3H, CH_3+CH_3]; ^{13}C-NMR (50.3 MHz) δ: 156.0; 153.6; 85.5; 75.5; 52.6; 52.3; 47.8; 39.2; 25.7; 14.5; 11.2. MS *m/z*: 196(2); 171(7); 170(33); 139(100); 93(9); 59(35). $[\alpha]^{21}_D$ = -84.4 (*c* = 0.84, $CHCl_3$). Anal. Calcd. for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.21; H, 7.52; N, 6.19.

(S)-Methyl 4-(methoxycarbonylamino)-5-phenyl-2-pentynoate (**7d**). A solution of (**6d**) (316 mg, 0.8 mmol) in THF (6 mL) was reacted with BuLi (1.7 mL, 2.7 mmol) and with 224 mg (2.4 mmol) of CH_3OCOCl. After work-up 265 mg of crude (**4d**) was obtained.

(**4d**): ^{1}H-NMR (200 MHz) δ: 7.32-7.16 [m, 5H, 5xCH ar]; 5.54-5.46 [m, 1H, CH-N]; 3.77 [s, 3H, OCH_3]; 3.76 [s, 3H, OCH_3]; 3.30-3.23 [m, 2H, CH_2]; 1.48 [s, 9H, 3xCH_3].

The crude product (250 mg) was refluxed in MeOH/HCl for 5 h. Evaporation of the solvent and purification (eluent: petroleum ether/ethyl acetate 2/1) afforded 92 mg (46%) of pure (**7d**).

(**7d**): ^{1}H-NMR (200 MHz) δ: 7.39-7.23 [m, 5H, 5xCH ar]; 5.02-4.71 [m, 1H+1H, NH+CH-N]; 3.74 [s, 3H, OCH_3]; 3.66 [s, 3H, OCH_3]; 3.06-2.94 [m, 2H, CH_2]; ^{13}C-NMR (50.3 MHz) δ: 155.5; 153.5; 135.1; 129.6; 128.6; 127.3; 86.0; 75.5; 52.7; 52.5; 44.1; 40.8. MS *m/z*: 230(2); 202(7); 170(43); 115(20); 91(100); 82(44). $[\alpha]^{22}_D$ = -42.6 (*c*=1.06, $CHCl_3$). Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.34; H, 5.72; N, 5.39.

(S)-Methyl 4-(methoxycarbonylamino)-6-methyl-2-heptynoate (**7e**). A solution of (**6e**) (370 mg, 1.0 mmol) in THF (10 mL) was reacted with BuLi (2.1 mL, 3.4 mmol) and with 383 mg (4.0 mmol) of CH_3OCOCl. After work-up 311 mg of crude (**4e**) was obtained.

(**4e**): ^{1}H-NMR (200 MHz) δ: 5.38-5.31 [m, 1H, CH-N]; 3.84 [s, 3H, OCH_3]; 3.76 [s, 3H, OCH_3]; 1.96-1.53 [m, 1H+2H, CH+CH_2]; 1.53 [s, 9H, 3xCH_3], 0.94 [d, 6H, *J* = 6.6 Hz, 2xCH_3]. The crude product (204 mg) was refluxed in MeOH/HCl for 5 h. Evaporation of the solvent and purification (eluent: petroleum ether/ethyl acetate 2/1) afforded 58 mg (39%) of pure (**7e**).

(**7e**): ^{1}H-NMR (200 MHz) δ: 4.90 [bd, 1H, *J* = 7.2 Hz, NH]; 4.69-4.59 [m, 1H, CH-N]; 3.75 [s, 3H, OCH_3]; 3.68 [s, 3H, OCH_3]; 1.85-1.67 [m, 1H, CH]; 1.62-1.48 [m, 2H, CH_2]; 0.92 [d, 6H, *J* = 6.6 Hz, 2xCH_3]. ^{13}C-NMR (50.3 MHz) δ: 155.9; 153.7; 87.0; 74.5; 52.7; 44.1; 41.6; 27.8; 24.7; 22.2; 21.9. MS *m/z*: 196(15); 171(80); 170(100); 168(36); 139(85); 59(83). $[\alpha]^{20}_D$ = -76.5 (*c* = 0.80, $CHCl_3$). Anal. Calcd. for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.26; H, 7.57; N, 6.19.

(R)-2,2-Dimethyl-3-benzyloxycarbonyl-4-(2,2-dibromoethenyl)-oxazolidine (**6f**). Powdered Zn (680 mg, 10.4 mmol), PPh_3 (2.72 gr 10.4 mmol) and CBr_4 (3.44 gr 10.4 mmol) were mixed together, suspended in CH_2Cl_2 (30 mL) and left to react for 30 h [7]. A solution of aldehyde (**2f**) (1.36 gr, 5.2 mmol) in CH_2Cl_2 (5 mL) was added to the reagent and stirred for 16 h. The mixture was diluted with pentane, the resulting black residue filtered and extracted with CH_2Cl_2, two times. The solutions were collected together and evaporated and the crude eluted on SiO_2 (eluent: CH_2Cl_2) to afford 1.77 gr (81%) of (**6f**).

(**6f**): ^{1}H-NMR (300 MHz, $CDCl_3$, T = 50°C): 7.4-7.3 [m, 5H, 5xCH ar]; 6.46 [d, 1H, *J*=8.1 Hz, C=CH]; 5.14 [q AB system, 2H, *J* = 12.3 Hz, CH_2Ph], 4.7-4.6 [m, 1H, CH], 4.10 [dd, 1H, *J* = 6.3 Hz, *J* = 9.3 Hz, CH_2]; 3.81 [dd, 1H, *J* = 2.5 Hz, *J* = 9.3 Hz, CH_2]; 1.61 [s, 3H, CH_3]; 1.52 [s, 3H, CH_3]. ^{13}C-NMR (50.3 MHz): 152.0; 137.4; 136.2, 128.5, 128.2, 128.1, 94.8; 91.3; 67.5; 66.8; 59.2; 26.3; 23.6. MS *m/z*: 402/404/406(1/3/1); 357/359/361 (3/3/2); 144(3); 91(100); 77(7). $[\alpha]^{19}_D$ = +31.8 (*c* = 0.9, $CHCl_3$).

(R)-2,2-Dimethyl-3-benzyloxycarbonyl-4-ethynyloxazolidine (**3f**). A solution of (**6f**) (1.56 g, 3.7 mmol) in THF (30 mL) was cooled at -78 °C. BuLi (4.6 mL 7.4 mmol) was added dropwise and left to react for 30 min. After hydrolysis with NaOH (0.01 M) and work-up 992 mg of crude were obtained. For analytical purposes 83 mg of this mixture were purified. Silica gel was treated with 5% $AgNO_3$ aqueous solution and dried in the oven overnight, a solution of the crude was eluted through a 10 cm column (eluent: petroleum ether/ethyl acetate = 5/1). Silica gel was then washed with MeOH and the solvent was evaporated. The residue was dissolved in concentrated NH_3 and extracted with ether. Evaporation afforded 32 mg (37%) of (**3f**) as a colorless oil.

(**3f**): ^{1}H-NMR (300 MHz, $CDCl_3$, T = 50°C): 7.4-7.3 [m, 5H, 5xCH ar]; 5.19 [q AB system, 2H, J = 12.4 Hz, CH_2Ph], 4.7-4.6 [m, 1H, CH], 4.1-4.0 [m, 2H, CH_2]; 2.29 [d, 1H, *J* = 2.4 Hz, C≡CH]; 1.66 [s, 3H, CH_3]; 1.52 [s, 3H, CH_3]. ^{13}C-NMR (50.3 MHz): 151.7; 136.4, 128.5, 128.2, 127.8 , 94.9; 82.3; 70.9; 69.0; 66.7; 48.0; 25.8; 24.0. MS *m/z*: 244(9); 200(8); 91(100); 77(6); 65(10). $[\alpha]^{22}_D$=-103.3 (*c* = 0.9,$CHCl_3$). IR (cm^{-1}): 3313 cm^{-1}.

(R)-Methyl (2,2-dimethyl-3-(benzyloxycarbonyl)-oxazolidin-4-yl)-propynoate (**1f**). The crude from the precedent step (808 mg) was dissolved in THF (25 mL) and cooled at - 78 °C, then reacted with 1.90 mL (3 mmol) of BuLi for 30 min and with 310 mg (3.3 mmol) of freshly distilled ClCOOMe. The reaction mixture was left at -78° C for 1 h. After work-up 1.13 g of crude were obtained and purified (petroleum ether/ethylacetate = 3/1) to afford 471 mg (1.5 mmol) of (**1f**) as a colorless oil (yield 41% from (**6f**)).

(**1f**): ^{1}H-NMR (300MHz, T=50°C): 7.4-7.3 [m, 5H, 5xCH ar]; 5.19 [q AB system, 2H, *J* = 12.2 Hz, CH_2Ph], 4.8-4.7 [m, 1H, CH]; 4.10 [app d, 2H, *J* = 2.6 Hz, CH_2]; 3.77 [s, 3H, OCH_3]; 1.66 [s, 3H, CH_3]; 1.53 [s, 3H, CH_3]. ^{13}C-NMR (75.45 MHz): 159.4; 152.8; 135.9; 128.4; 128.0; 127.8; 95.3; 84.5; 74.2; 68.1; 67.1; 528; 48.1; 25.9; 24.0. MS *m/e*: 302(1); 258(7); 183(2); 91(100); 57(10). IR: 1715. $[\alpha]^{20}_D$ = -144.3 (*c* = 0.96 $CHCl_3$). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.28; H, 6.00; N, 4.28.

(R)-Methyl 4-(benzyloxycarbonylamino)-5-hydroxy-2-pentynoate (**11**). A solution of (**1f**) (319 mg, 1 mmol) in 10 mL of MeOH/H_2O (10/1) was refluxed overnight together with 194 mg (1 mmol) of PTSA. A slight excess of PTSA (100 mg, 0.5 mmol) was then added and the mixture stirred for more. MeOH was evaporated and the residue was dissolved with ether. The organic phase was washed with brine, dried and evaporated to afford 252 mg of pure (**11**) (91%).

(**11**): m.p. = 73-75 °C. ^{1}H-NMR (200 MHz) δ: 7.5-7.2 [m, 5H, 5xCH ar]; 5.60 [bd, 1H, *J* = 8.8 Hz, NH]; 5.2-5.1 [m, 2H, CH_2Ph]; 4.8-4.7 [m, 1H, CH]; 3.9-3.6 [m, 2H+3H, OCH_2+OCH_3]; 2.83 [bs, 1H, OH]. ^{13}C-NMR (75.45 MHz) δ: 155.6; 153.5; 135.8; 128.5; 128.3; 128.2; 84.4;

75.4; 67.4; 64.3; 52.9; 45.5. MS *m/z*: 215(4); 186(1); 139(13); 108(19); 91(100); 77(7). $[\alpha]^{20}_D$ = -42.4 (*c* = 1.0, $CHCl_3$).

Synthesis of the Mosher's Esters of (**11**). Anhydrous pyridine (0.3 mL), CCl_4 (0.5 mL) and (*S*)-MTPA chloride (25 mg, 0.1 mmol) were mixed together and reacted at rt for 1 h with (*R*)-(**11**). (25 mg, 0.1 mmol). After work-up the residue was analyzed by ^{1}H NMR. Diastereomer (*1S*),(*2R*) was recovered with e.e. > 95%. ^{1}H-NMR (200 MHz) δ:3.54 (q, 3H, *J*=1.6 Hz); ^{19}F-NMR (282.2 MHz) δ:-72.27 (s, 3H).

The reaction was repeated with (*R*)-MTPA chloride affording diastereomer (*1R*),(*2R*) with e.e > 95%. ^{1}H-NMR (200 MHz) δ:3.52 (q, 3H, *J*=1.4 Hz);^{19}F-NMR (282.2 MHz) δ:-72.33 (s, 3H).

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References

1. Corriu, R. J. P.; Bolin, G.; Iqbal, J.; Moreau, J. E.; Vernhet, C. *Tetrahedron* **1993,** *49*, 4603.
2. Corriu, R. J. P.; Huynh, V.; Iqbal, J.; Moreau, J. J. E.; Vernhet, C. *Tetrahedron* **1992,** *48*, 6231.
3. Reginato, G.; Capperucci, A.; Degl'Innocenti, A.; Mordini, A.; Pecchi, S. *Tetrahedron* **1995,** *51*, 2129.
4. Abdulganeeva, S. A.; Erzhanov, K. B. *Zh. Org. Kim. CA 110:114289* **1988,** *24*, 1772.
5. Reginato, G.; Mordini, A.; Degl'Innocenti, A.; Caracciolo, M. *Tetrahedron Lett.* **1995,** *36*, 8275.
6. Reginato, G.; Mordini, A.; Caracciolo, M. *J. Org. Chem.* **1997,** *62*, 6187.
7. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972,** *12*, 3769-3772.
8. Garner, P.; Park, J. M. *Org. Synth.* **1991,** *70*, 18.
9. Reetz, M. T.; Strack, T. J.; Kanand, J.; Goddard, R. *Chem. Commun.* **1996**, 733.
10. Reginato, G.; Mordini, A.; Messina, F.; Degl'Innocenti, A.; Poli, G. *Tetrahedron* **1996,** *52*, 10985.
11. Takano, S.; Setoh, M.; Yamada, O.; Ogasawara, K. *Synthesis* **1993**, 1253.
12. Beaulieu, P. L.; Schiller, P. W. *Tetrahedron Lett.* **1988,** *29*, 2019.
13. Beak, P.; Lee, W. K. *J. Org. Chem* **1993,** *58*, 1109.
14. Branquet, E.; Meffre, P.; Durand, P.; Le Goffic, F. *Synth. Comm.* **1998,** in press.
15. Dole, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973,** *95*, 512.
16. Still, W. C.; Kahn, M. K.; Mitra, A. *J. Org. Chem.* **1978,** *43*, 293.