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En Route to Optically Active Ethynylglycine Derivatives[1]

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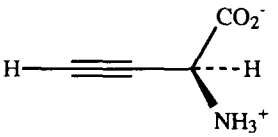
Abstract : First results in the synthesis of chiral non racemic ethynylglycine derivatives from protected L-serinal are described.

Ethynylglycine **1** (FR 900130) is a naturally occuring unusual α-aminoacid isolated from fungus *Streptomyces Catenulae* in 1980.[2] This notoriously labile compound is obtained as an hygroscopic 70% pure powder in a very low yield. It has been characterized as its N-acetyl derivative and the structure has been determined to be L-2-amino-3-butynoic acid.[2]



1

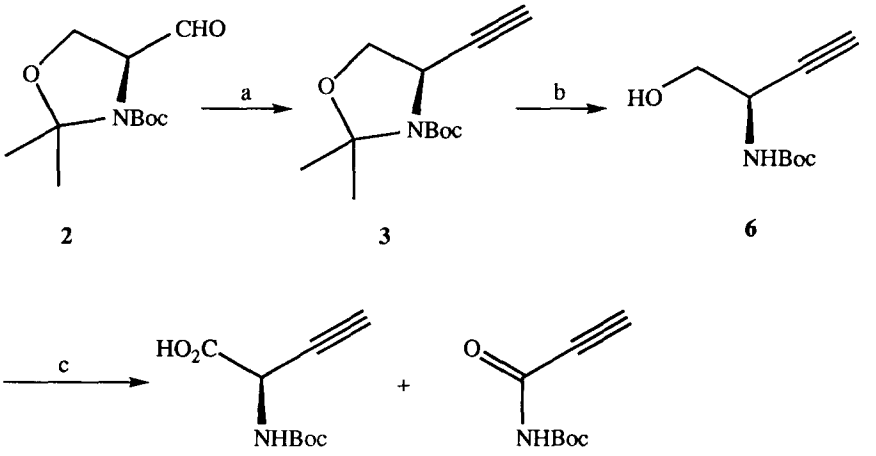
It displays antimicrobial activity against gram positive bacteria which could be explained by its inhibitory activity on L-alanine racemase.[2a,3]

More stable protected derivatives of **1** have been synthesized in racemic form.[4] In this report, we describe the first synthesis of chiral non racemic ethynylglycine derivatives.

Protected L-serinal **2** now available in large quantities and in good yield from L-serine[5] was selected as a configurationally stable optically pure starting material (scheme).

We first attempted the conversion of aldehyde **2** into alkyne **3** using the two steps transformation (PPh_3, CBr_4 then BuLi) described by Corey and Fuchs[6] but these conditions resulted in low yields (<25% yield in **3** based on **2**) and/or decomposition as already reported for other substrates.[7,8] The one-step transformation (dimethyl diazomethyl phosphonate **4**, tBuOK) described by Gilbert[9] worked quite well (60% yield in **3**) but **4** proved to be tricky to synthesize. Finally, direct conversion of aldehyde **2** into alkyne **3** was performed in good yield with the mild method described by Ohira using readily available dimethyl 1-diazo-2-oxopropyl phosphonate **5**.[10]

Obtention of N-Boc amino alcohol **6** was best performed by simultaneous Boc and oxazolidine solvolysis with TFA followed by reprotection of the amine with di-*tert*-butyl dicarbonate.[11] Enantiomeric purity of **6** was ascertained by ^{19}F NMR spectroscopy of Mosher's ester derivatives (ee>90%).



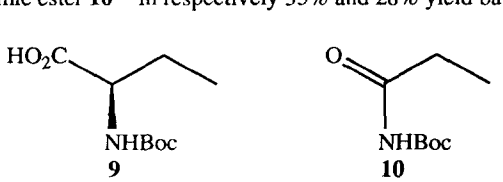
a - $CH_3COC(N_2)P(O)(OMe)_2$ **5** : 1.5 eq., K_2CO_3 : 2eq. , MeOH, argon, 0°C-rt, 75-85% ; b - TFA / MeOH : 10/1, 0°C-rt then BocOBoc : 2.5 eq., Na_2CO_3 : 2.5 eq., dioxanne, H_2O (pH 8-9), 0°C , 80-90% ; c - Jones' oxidation, 70%.

Scheme

The oxidation of **6** to N-Boc-D-ethynylglycine **7** proved to be the most challenging step. The presence of the alkyne function in such a position and its propensity to form allene precluded the usual procedures to perform such a transformation.[12a-c] Among others, PDC in DMF[12a] , standart Jones' oxidation[12a,d-f], TEMPO/$NaClO_2$[12g], Pt/O_2[12h], PCC/NaCN[12i] have been tried and either extensive decomposition or no reaction were observed. Ultimately, the best conditions found were the Jones' oxidation under inverse addition method (alcohol added to Jones' reagent)[13]. N-Boc-D-ethynylglycine **7** is thus formed together with the side product[14] **8** (**7** : **8** ≈ 1.5 : 1, 70% overall yield based on **6**, $[\alpha]_D^{20}$=-23 to -26, c=1, CH_2Cl_2). Adding manganous salts[14] to diminish the amount of **8** in the reaction mixture made no difference.

Unfortunately, all the attempts to purify **7** using standard procedures (mild acido-basic treatment, silica gel flash chromatography, preparative layer chromatography on cellulose) failed because of its inherent lability. Structure of **7** was confirmed by ^1H, ^{13}C NMR, IR, mass spectrometries.[15]

Catalytic hydrogenation of crude **7** led to optically active (R)-2-*tert*-butoxycarbonylamino butyric acid **9** and to carbamic ester **10**[16] in respectively 33% and 28% yield based on **6**.[15]



9 **10**

The methyl ester derivative of **9** was shown to be 93% ee by enantioselective capillary GC analysis (XE-60-S-val-(S)-α-pea column, temperature 115°C, L=50 m, carrier gas : 2 bars He).

Therefore, we have demonstrated that this route can lead to optically active ethynylglycine derivatives. Improvements are under investigation and complete results will be reported elsewhere.

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15. For all compounds, spectral data were consistent with the assigned structures, literature data and/or comparison with authentic samples. Physical data for compounds **6**, **7**, **8**, and **9** : **6**: m.p.=77-78°C, $[\alpha]_D^{20}$=-41 to -43 (c=1, $CHCl_3$), ^1H NMR (200MHz, $CDCl_3$): δ 1.46 (s, 9H), 2.34 (d, J=2.4Hz, 1H), 2.45 (t, J=6.5Hz, 1H), 3.73 (dd, J=4.6Hz, 6.5Hz, 2H), 4.53 (br, 1H), 5.06 (br, 1H) ; ^{13}C NMR (50MHz, $CDCl_3$): δ 28.2, 45.1, 65.4, 72.3, 80.4, 80.7, 155.2 ; MS (DCI, NH_3) : 203, 186, 147, 130 ; Anal. Calcd for $C_9 H_{15} N O_3$: C, 58.36 ; H, 8.16 ; N, 7.56. Found: C, 58.34 ; H, 7.82 ; N, 7.49. **7**: ^1H NMR (200MHz, $CDCl_3$): δ 1.46 (s, 9H), 2.42 (d, J=2.7Hz, 1H), 5.14 (dl, 1H), 5.30 (dl, 1H), 7.86 (br, 1H); ^{13}C NMR (50MHz, $CDCl_3$): δ 27.8, 45.3, 72.7, 80.5, 83.8, 155.0, 170.2. **8**: ^1H NMR (200MHz, $CDCl_3$): δ 1.52 (s, 9H), 3.29 (s, 1H), 6.35 (br, 1H); ^{13}C NMR (50MHz, $CDCl_3$): δ 28.1, 75.6, 80.8, 83.8, 149.0, 151.0. **7+8** : IR (neat) : 3400, 3300, 3020, 2980, 2120, 1765, 1720, 1680 cm^{-1}. MS (DCI, NH_3): 217, 200, 187, 161, 144, 131. **9**: $[\alpha]_D^{20}$=+4.5 (c=2.5, CH_2Cl_2), optically pure compound[17]: $[\alpha]_D^{20}$=+9.5 (c=2.2, CH_2Cl_2)
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