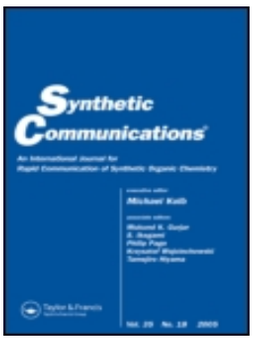

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SYNTHESIS OF NEW CHIRAL VINYL HALIDES FROM L-SERINAL

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Abstract : The synthesis of new chiral and functionalized vinyl halides from protected L-serinal is described.

Vinyl halides and terminal alkynes are interesting intermediates in the synthesis of more complex molecules with biological values and are obtained by different routes.[1] They are for instance good substrates for metal-catalyzed couplings.[2]

We described recently the first synthesis of optically active ethynylglycine derivatives from L-serinal **1** using alkyne **2** as key intermediate (Scheme 1). The latter compound was obtained in one step by ethynylation of **1** with dimethyl 1-diazo-2-oxopropyl phosphonate.[3] The Corey-Fuchs method[4] using dibromovinyl intermediate **3**[5] has also been used to synthesize **2** from **1**. As reported before on

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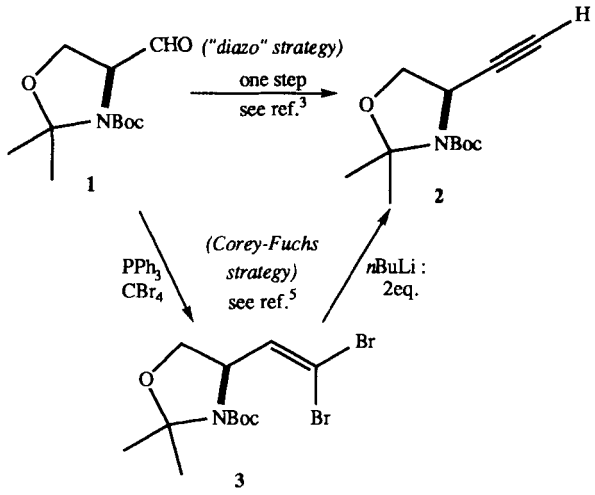
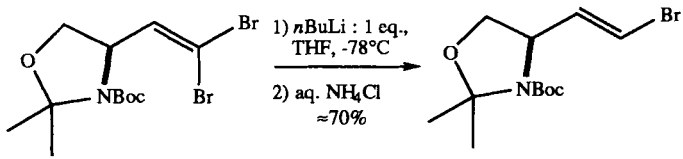
other sensitive substrates, this reaction proved to be cumbersome in our hands and prompted improvements of the procedure.[6] Alkyne **2** could have also been obtained via *n*BuLi promoted elimination on monochloro vinyl derivatives.[7]



Scheme 1

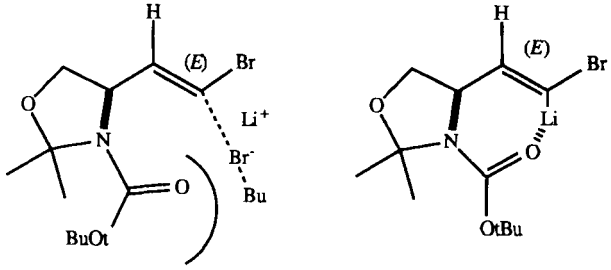
In that respect, we wish to report our results on the synthesis of new highly functionalized vinyl bromides **4** and **7** and vinyl chlorides **5**, **6** and **8** derived from L-serinal **1**.[8] When dibromovinyl derivative **3** is treated with 1 eq. *n*BuLi, major formation of (E)-vinyl bromide **4** is observed, contaminated with terminal alkyne **2** (**4/2**= 9/1)(Scheme 2).



3 **4**

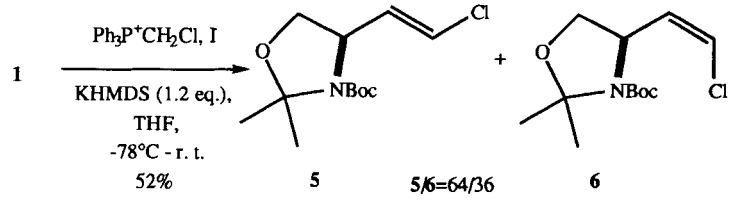
Scheme 2

Exclusive formation of (*E*) isomer has recently been observed in similar reactions.[9] These results could be explained because strain relief is expected due to elongation of the carbon-bromine bond in the reaction at the more hindered bromine atom (see intermediate **A**), or by preferential formation of (*E*)-bromovinyllithium intermediate **B** possibly stabilized by Boc neighbouring group participation.[10, 11]



A **B**

Vinyl chlorides **5** and **6** were obtained from **1** by a Wittig reaction (Scheme 3). All attempts to increase the yield or reverse the ratio of separable isomers **5** and **6** failed: tBuOK(1.1 eq.), THF, reflux, yield: 40%, **5/6**= 70/30 ; *n*BuLi (1.2 eq.), THF, -78°C-r.t., yield: 30%, **5/6**= 60/40.

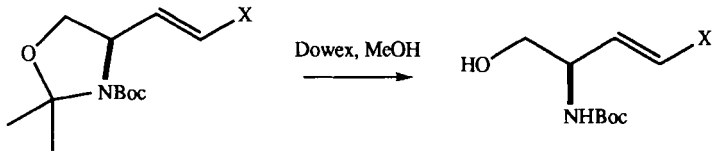


Scheme 3

As expected[12], we observed that *n*BuLi elimination of the (*Z*) isomer **6** is faster than the (*E*) isomer **5**. In the favorable former case (*n*BuLi : 2.1 eq., THF, -78°C)

a maximum yield of 20% of isolated **2** is observed and in the latter case (*n*BuLi : 3 eq., THF, -78°C), degradation occured.[13]

Oxazolidines **4, 5** were selectively deprotected into the N-protected 2-amino alcohols **7, 8** using a Dowex H^+ resin in good yield (Scheme 4).[14]
NMR analysis of Mosher ester derivatives[15] of alcohols **7** and **8** showed the enantiomeric purity to be greater than 90%.



4, X=Br
5, X=Cl

7, X=Br, 72%
8, X=Cl, 74%

Scheme 4

EXPERIMENTAL

Unless otherwise noted, all solvents and reagents were used as purchased. L-serinal **1** (also called "Garner aldehyde")[16] and dibromovinyl derivative **3**[4, 5] were synthesized following literature procedures. TLC conditions : silica gel 60F254 plates ; visualization obtained by treating the plate with trifluoroacetic acid fumes followed by spraying with an alcoholic ninhydrin solution and heating the plate. Commercial *n*BuLi solutions were extemporaneously titrated according to the Suffert's method[17] and tetrahydrofuran freshly distilled from sodium / benzophenone ketyl prior to use.
^1H and ^{13}C NMR spectra were recorded on a 200 MHz Brucker at room temperature using chloroform-*d* as solvent. In these conditions, the oxazolidines

exist as slowly interconverting rotamers which explains that some signals are split or broad. Chemical shifts (δ) are given in parts per million (ppm) downfield from tetramethylsilane and coupling constants (J) in Hz. The following abbreviations are used : s=singlet, d=doublet, m=multiplet, br=broad. Melting points were measured using a Mettler FP 61 apparatus. Optical rotations were measured using a Perkin Elmer Model 241 polarimeter using chloroform as solvent. Mass spectra were obtained on a Ribermag R10 10 by chemical ionisation with NH_3 as reactant gas. The chlorine (^{35}Cl and ^{37}Cl) and bromine (^{79}Br and ^{81}Br) isotopy is observed on all the halogenated fragments. Only the fragments of ^{35}Cl and ^{79}Br are indicated below.

The stereochemistries of all the products were determined by coupling constants of the olefinic protons in proton NMR spectra (typically, $^3J_{cis}$~6-7Hz and $^3J_{trans}$~12-14Hz for vinyl chlorides and bromides).[18]

(R)-(E)-4-(2-Bromoethenyl)-2,2-dimethyl-3-oxazolidinecarboxylic acid 1,1-dimethylethyl ester 4.

Under argon, 1.5 ml of *n*BuLi (1.7M in hexane, 2.6 mmol) are slowly added to a cooled stirred solution of 1 g (2.6 mmol) of **3** at -78°C in anhydrous THF (10 ml). After a further 15 min at -78°C, the mixture is quenched with MeOH (10ml). A saturated aqueous NH_4Cl solution (10ml) is added. The organic phase is washed with a saturated aqueous NaCl solution (10ml), and the aqueous phase is extracted with ether (20ml). After drying ($MgSO_4$) and evaporation of the combined organic phases, the residue is purified by flash silica gel chromatography (eluent : pentane / ethyl acetate = 9 / 1) to obtain 0.55 g of non-separable mixture of **4** and **2** (**4/2**=9/1) (70 %) as a colorless oil.

4: ^{1}H-NMR (δ) 1.48 (s, 9H); 1.62, 1.65 (2s, 6H); 3.78 (dd, 9Hz, 1.7Hz, 1H); 4.05 (dd, 9Hz, 5.1Hz, 1H); 4.2 (br, 1H); 5.75 (dd, 12.5Hz, 8.9Hz, 1H); 5.95 (d, 12.5Hz, 1H). MS : 323 $(M+NH_4)^+$, 306 $(M+H)^+$, 267 $(M-t\text{Bu}+NH_4)^+$.

(R)-(E)-4-(2-Chloroethenyl)-2,2-dimethyl-3-oxazolidinecarboxylic acid 1,1-dimethylethyl ester 5 and (R)-(Z)-4-(2-chloroethenyl)-2,2-dimethyl-3-oxazolidinecarboxylic acid 1,1-dimethylethyl ester 6.

To a stirred suspension of 3.5 g (10 mmol) of chloromethylene triphenylphosphonium chloride in anhydrous THF (50 ml) at -20°C is slowly added 20 ml of KHMDS (0.5M in toluene, 10 mmol). After 1h at -20°C, the deep orange solution is cooled to -70°C. Then 2.3g (10 mmol) of L-serinal **1** in THF (10 ml) is added dropwise, left to react at -70°C for 1h then allowed to warm to r.t. for 3h. The reaction mixture is hydrolyzed by a saturated aqueous NH_4Cl solution (20ml). The organic phase is washed with brine (20ml). The combined aqueous phases are extracted twice with diethyl ether (30ml). The combined organic phases are dried ($MgSO_4$) and concentrated to dryness. Triphenylphosphine oxide is separated by crystallization in diethyl ether at 0°C, and the filtrate is concentrated. The yellow oily residue is purified by flash silica gel chromatography (eluent : pentane/ethyl acetate= 9/1). 0.49 g (19%) of **6** and 0.86 g (33%) of **5** are successively obtained.

5: oil, $[\alpha]_D^{20}$=-31.8 (c 0.22, $CHCl_3$). ^{1}H-NMR (δ) 1.45 (s, 9H); 1.62, 1.65 (2s, 6H); 3.78 (dd, 9.1Hz, 1.9Hz, 1H); 4.05 (dd, 9.1Hz, 5.9Hz, 1H); 4.3-4.4 (br, 1H); 5.92 (dd, 13.5Hz, 8.3Hz, 1H); 6.1-6.3 (br, 1H). ^{13}C-NMR (δ) 151, 132, 121, 94, 80, 67, 57, 28, 27, 26, 24, 23. MS : 279 $(M+NH_4)^+$, 262 $(M+H)^+$, 223 $(M-t\text{Bu}+NH_4)^+$, 206 $(M-t\text{Bu}+H)^+$.

6: oil, $[\alpha]_D^{20}$=+60 (c 0.2, $CHCl_3$). ^{1}H-NMR (δ) 1.48 (s, 9H); 1.52, 1.65 (2s, 6H); 3.78 (dd, 2.6Hz, 8.9Hz, 1H); 4.16 (dd, 6.1Hz, 8.9Hz); 4.9 (br, 1H); 5.86 (brt,~7Hz, 1H); 6.11-6.13 (brd, ~7Hz, 1H).^{13}C-NMR (δ) 151, 132, 119, 94, 79, 67, 54, 28, 26, 23.

(2R)-(3E)-2-[(1,1-dimethylethoxy)carbonyl amino]-4-chloro-but-3-en-1-ol 8

In a solution of 0.5g (1.9mmol) of oxazolidine **5** in methanol (15 ml), ca. 1mL of methanol-washed DOWEX 50W strong H^+ resin is added and the mixture is stirred overnight at room temperature. TLC analysis shows completion of the reaction. The mixture is filtered, the resin washed with methanol. The filtrate is diluted with dichloromethane (20 ml) and washed with a saturated aqueous bicarbonate solution (5 ml), dried over magnesium sulfate and concentrated to dryness under reduced pressure to give 0.31 g (74%) of **8** as an pure oil (TLC analysis : pentane/ ethyl acetate : 6/4, Rf=0.4).

$[\alpha]_D^{20}$=+45.0 (c 0.59, $CHCl_3$). ^{1}H-NMR (δ) 1.45 (s, 9H); 3.6-3.8 (m, 2H); 4.25 (brs, 1H); 4.94 (brd, ~7Hz, 1H); 5.93 (dd, 13.4Hz, 6.7Hz, 1H); 6.27 (dd, 13.4Hz, 1.3Hz, 1H). ^{13}C-NMR (δ) 155, 130, 121, 80, 65, 53, 28. MS : 239 $(M+NH_4)^+$, 222 $(M+H)^+$, 183 $(M-t\text{Bu}+NH_4)^+$, 165 $(M-t\text{Bu}+H)^+$.

(2R)-(3E)-2-[(1,1-dimethylethoxy)carbonylamino]-4-bromo-but-3-en-1-ol 7.

Same procedure as above. yield : 72% (oil). TLC analysis : pentane / ethyle acetate: 7/3, Rf=0.5). $[\alpha]_D^{20}$=-112 (c 0.2, $CHCl_3$). ^{1}H-NMR (δ) 1.45 (s, 9H); 3.6-3.8 (m,

2H); 4.2-4.3 (m, 1H); 4.95 (brd, ~7.5Hz, 1H); 6.20 (dd, 13.9Hz, 6.2Hz, 1H); 6.39 (d, 13.9Hz, 1H). ^{13}C-NMR (δ) 155, 135, 109, 80, 64, 54, 28. MS (DCI, NH_3) : 266 $(M+H)^+$, 227 $(M-t\text{Bu}+NH_4)^+$, 210 $(M-t\text{Bu}+H)^+$, 186 $(M-Br)^+$.

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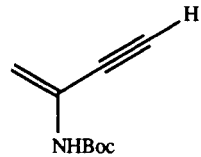
10. For a stereoselective synthesis of (Z)-vinyl bromides see ref. 2c.
11. In our hands, alkyne **2** is obtained with a maximum 50% yield when 2eq. *n*BuLi is added slowly on a THF solution of dibromovinyl derivative **3**, at -78°C. **2** is often contaminated with vinyl bromide **4** and with enamine **9**.[5a] Formation of **9** is probably due to abstraction of the proton with enhanced acidity α to NBoc (see Beak, P. ; Lee, W.-K. *Tetrahedron Lett.* **1989**, *30*, 1197) with concomitant acetone elimination. We also observed this reaction with other oxazolidines derived from L-serinal **1** with a double or a triple bond in the 4-position.[3b] Unstable enamine **9** is obtained in 65% yield if alkyne **2** is treated with excess *n*BuLi in THF.

9 : ^{1}H-NMR (200MHz, $CDCl_3$, δ in ppm): 1.49 (s, 9H); 2.88 (s, 1H); 5.05 (s, 1H); 5.82 (s, 1H); 6.0 (brs, 1H). MS (DCI, NH_3) 185 $(M+NH_4)^+$, 168 $(M+H)^+$, 129 $(M-t\text{Bu}+NH_4)^+$.



9

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