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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

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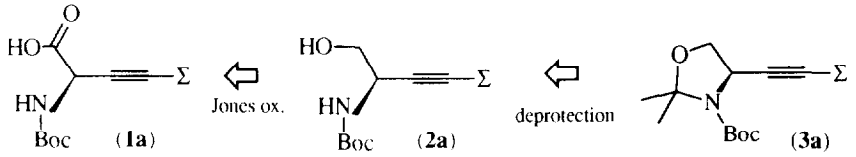
Abstract: *(R)-(-)-2,2-Dimethyl-3-t-butoxycarbonyl-4-ethynyl-oxazolidine* (**3a**) *has been prepared in good yield from chiral aminoaldehyde* (**4**) *through a two step procedure. Metalation of compound* (**3a**) *and subsequent reaction with electrophiles has been investigated leading to the stereoselective synthesis of a new series of substituted alkynes which can be considered as useful precursors of compounds of biological interest.*

We have recently shown that suitably protected propargylamines may act as useful precursors of highly functionalized allylic systems, through addition reaction with bis-metallic reagents[1]. In an extension towards more functionalized substrates we envisaged chiral propargylic systems bearing an amino acid residue on the lateral chain as interesting substrates to be tested. For this reason we had to device a new synthetic protocol for the stereoselective synthesis of suitably protected ethynyl glycine (**1a**) and its derivatives.

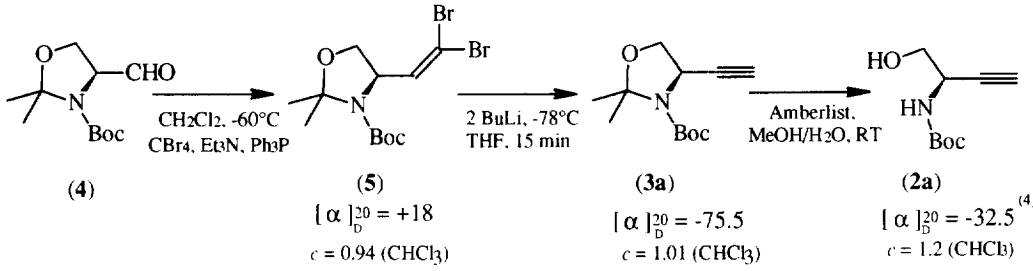


(**a**) Σ = H, (**b-i**) Σ ≠ H

Scheme 1

Compound (**1a**) is an antibiotic amino acid which was isolated for the first time in 1980[2] and is known to be very labile in the free form. There are very few reports[3] on the synthesis of its protected derivatives and none of them describe enantioselective procedures. While this work was in progress the first non racemic synthesis of compound (**1a**) was published[4]. This prompted us to forward our results on the enantiospecific synthesis of (*R*)-(-)-2,2-dimethyl-3-*t*-butoxycarbonyl-4-ethynyl-oxazolidine (**3a**) and its derivatives (**3b-i**), that we regarded as suitable and stable precursors of ethynylglycine and its γ-substituted derivatives. We thought in fact that, in order to circumvent the problems connected with the lability and the predictable low configurational stability of compound (**1a**), its corresponding oxazolidine derivative (**3a**) could constitute an alternative target.

It has been widely shown[5], that protected serinal derivatives are suitable starting material for the preparation of non-natural amino acids of opposite configuration: in particular compound (**3a**) has been used[4] as ethynilglycine precursor as outlined in Scheme 1, although this reactions sequence was only partially successful. We developed a new procedure for the synthesis of (**3a**) *via* the one carbon homologation of aldehyde (**4**), in two steps, following a recently published modification[6] of the method described by Corey and Fuchs[7]. Oxazolidine (**4**) is readily available[8], in enantiomerically pure form, from the naturally occurring (*S*)-(+)-serine by protection as oxazolidinic ester and reduction: treatment with dibromoethylene triphenylphosphorane in presence of triethylamine afforded the corresponding 1,1-dibromoalkene (**5**) which was isolated in a 82% yield and then quantitatively converted into the alkyne (**3a**), by reaction with 2 equivalents of BuLi at -78 °C [9] (Scheme 2). The reaction sequence can also be performed without isolation of the intermediate (**5**) and, after purification by flash chromatography, afforded compound (**3a**) in 74% overall yield.



(**4**)

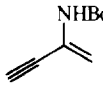
(**5**) $[\alpha]_D^{20} = +18$ (c = 0.94 $CHCl_3$)

(**3a**) $[\alpha]_D^{20} = -75.5$ (c = 1.01 $CHCl_3$)

(**2a**) $[\alpha]_D^{20} = -32.5$ [4] (c = 1.2 $CHCl_3$)

Scheme 2

This procedure is alternative to those recently[4] reported and allows the isolation, in reasonable yield, of (**5**) which is by itself an interesting synthetic intermediate. It has to be underlined that a careful control of the reaction conditions is necessary in order to avoid the formation of undesired by-products. We have observed, in fact, that prolonged reaction times or a large excess of base induced the formation of enamine (**6**) as predominant product.

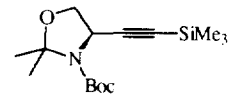
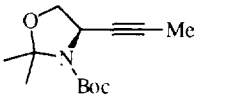
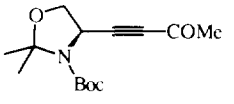
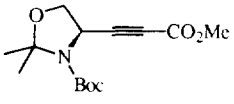
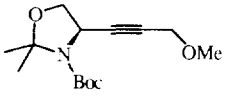
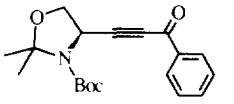
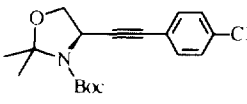
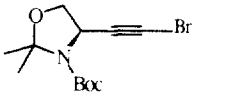


(**6**)

The above reaction sequence has been also performed starting with (*R*)-(-)-serine affording compound (**3a**) with the opposite configuration ($[\alpha]_D^{20} = +75$, c = 1.03 $CHCl_3$). The optical purity of (**3a**) showed to be >95% as established by ^{1}H-NMR analysis of the diastereomeric Mosher's esters[10] prepared by reactions of (*R*)-(-) and (*S*)-(+) α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) with (*R*)-(+)-amino alcohol (**2a**) obtained by deprotection of (**3a**) with Amberlyst in $MeOH/H_2O$ at room temperature. The two diastereomers were found to be clearly distinguishable and showed no contamination from racemized material: we could therefore conclude that along our synthetic sequence, no racemization occurred.

As a further step we investigated the behaviour of compound (**3a**) towards metalation with BuLi and further reaction with electrophiles in order to achieve a series of previously unreported chiral 4-ethynil-oxazolidine derivatives (**3b-f**).

Table 1 - Metalation of compound (**1a**) and subsequent reactions with electrophiles..

Electrophile	Product	Reaction conditions	$[\alpha]_D^{20}$	Conversion [a]
Me_3SiCl	 (**3b**)	THF, -78°C, 1 h	[+195] c = 0.64 ($CHCl_3$)	> 95% (53%)
MeI	 (**3c**)	THF, RT overnight	[-126][b] c = 0.80 ($CHCl_3$)	75%
MeCOCl	 (**3d**)	THF, $ZnCl_2$, -40°C, RT, 15 h	-	42%
CH_3OCOCl	 (**3e**)	THF, -78°C, 1 h	[-105] c = 1.10 ($CHCl_3$)	>95% (46%)
MOMCl	 (**3f**)	THF, -15°C, 3 h	-	86%
PhCOCl	 (**3g**)	Et_2NH, R.T. 4h $PdCl_2(PPh_3)_2$/CuI	[-111] c = 0.97 ($CHCl_3$)	>95 (70%)
p-CHO-C_6H_4-I	 (**3h**)	Et_3N, 50°C 2h $PdCl_2(PPh_3)_2$/CuI	[-185] c = 1.44 ($CHCl_3$)	70% (59%)
-	 (**3i**)	starting from (**5**), THF, -100°C NaHDMS, 45min	[+122][c] c = 1.09 ($CHCl_3$)	75%

a) Calculated by ^{1}H-NMR analysis of the crude mixture. In parenthesis yields of isolated products.
b) A small amounts of the crude was purified by semipreparative HPLC.
c) A portion of the crude was purified by bulb to bulb distillation.

As shown in Table 1 good yields of derivatives (**3b-f**)[11] are generally obtained except when acetylchloride was used as electrophile. This is probably due to the low reactivity of acyl chlorides towards lithium acetilides[12], which in our case was not enhanced after transmetalation with $ZnCl_2$ and is therefore responsible for the competitive formation of (**6**).

To circumvent this problem we decided to test a milder procedure which involves the direct coupling of (**3a**) with electrophiles in the presence of $PdCl_2(PPh_3)_2$/CuI[13]. Compounds (**3g**) and (**3h**) have been obtained[14]

in this way by reaction with benzoylchloride and *para*-iodo-benzaldehyde respectively. Furthermore, dehydroalogenation[6] of vinyldibromide (**5**) in the presence of sodium bis-trimethylsilyl amide (NaHMDS) afforded (**3i**) in good yield: this derivative is of particular interest as it can be regarded as a new chiral building blocks, being bromo-alkynes useful intermediates[15].

In conclusion we have reported the stereoselective synthesis of 2,2-dimethyl-3-*t*-butoxycarbonyl-4-ethynyl-oxazolidine (**3a**) and of a series of previously unknown derivatives (**3b-i**). The reactivity of these compounds is currently under investigation: in particular we presume that further elaboration on the lateral chain may lead to the synthesis of a variety of unsaturated amino acids precursors.

References and notes

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9. *Experimental procedure*: 290 mg (0.88 mmol) of CBr_4 are dissolved in CH_2Cl_2 (6 mL) and cooled at -20°C, a solution of 230 mg (0.88 mmol) of PPh_3 in CH_2Cl_2 (12 mL) is then added and left to react for 30 min. After this time the reaction mixture is cooled to -60°C and a solution of 100 mg (0.44 mmol) of (**3a**) and 0.62 mL (0.44 mmol) of Et_3N in CH_2Cl_2 (4 ml) is added. The reaction is left for 30 min at -60°C, then at room temperature overnight. The solution is then diluted with petroleum ether, then filtered over silica gel. After evaporation of the solvent 135mg (0.36 mmol) of pure (**5**) are obtained (82%). (**5**): ^{1}H-NMR (300 MHz, T=50°C) ($CDCl_3$) δ (ppm) 1.48 [s, 9H]; 1.52 [s, 3H,]; 1.60 [s, 3H,]; 3.78 [dd, 1H, J=9.3 J=2.7]; 4.10 [dd, 1H, J=6.6 J=9.30]; 4.4-4.6 [bm, 1H]; 6.46 [d, 1H, J=8.1]; ^{13}C-NMR (50.3 MHz) ($CDCl_3$) δ (ppm) 151.66; 138.54 ; 94.51; 89.94 ; 80.44; 67.38; 59.53; 28.49; 26.28, 23.88. MS m/z (%) 32 (31); 41 (15); 57 (100; $C(CH_3)_3^+$); 84 (89); 86 (57); 149 (20); 314 (19); 316 (10) [M^+- CH_3- CH_2=$C(CH_3)_2$]. $[\alpha]_D^{20}$ = +18, (*c* = 1 $CHCl_3$); m.p. = 55-56°C.

   125 mg (0.32 mmol) of (**5**) are dissolved in anhydrous THF (3 ml) and cooled to -78°C, 0.410 mL of BuLi 1.6 M in hexane (0.64 mmol) are slowly added, left to react for 40 min and then hydrolyzed with a 0.01M NaOH solution. After workup and evaporation of the solvent 77 mg of crude (**3a**) are recovered. After flash chromatography (eluent: petroleum ether/ethyl acetate =10/1) 57 mg (0.25 mmol) of (**3a**) are obtained (78%): ^{1}H-NMR (300 MHz, T=50°C) ($CDCl_3$) δ (ppm) 1.50 [s, 9H,]; 1.63 [s, 6H]; 2.26 [d, 1H, J=2.1]; 3.98-4.08 [m, 2H]; 4.45-4.60 [bm, 1H,]; ^{13}C-NMR (50.3 MHz, T = 50°C) ($CDCl_3$) δ (ppm) 24.78; 26.27; 28.43; 48.43; 68.75; 70.24; 80.56; 82.77; 94.38; 151.51; MS m/z (%) 41 (89); 42 (23); 43 (36); 52 (12); 57 (100) [$C(CH_3)_3^+$)]; 58 (16); 59 (24); 66 (12); 67 (12); 68 (17); 79 (14); 94 (18); 110 (100) [$C_6H_8NO^+$]; 111 (11); 152 (16); 154 (100); 210 (33); [M^+- CH_3)]; IR: (film) 3308; 1696; $[\alpha]_D^{20}$ = -73.5 (*c* = 1, $CHCl_3$).
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11. *Typical procedure*: Oxazolidine (**3a**) is dissolved in THF and the solution is cooled to -78°C, 2 equivalents of BuLi 1.6 M in hexane are then slowly added and left to react for 30 minutes. The reaction mixture is warmed to -15°C, left at this temperature for 15 minutes and then 1 equivalent of the desired electrophile is added and left to react as shown in table 1. After hydrolytic workup the crude product is purified by flash chromatography.
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13. Takahashi, S., Kuroyama, Y., Sonogashira, S., Hagihara, N., *Synthesis*, **1980**, 627.
14. *Typical procedure*: Oxazolidine (**3a**) is dissolved in the appropriate amine, then the electrophile is added at room temperature with CuI and $PdCl_2(PPh_3)_2$ (10%). After the reaction is completed the solvent is evaporated, the crude product is diluted with ether and filtered over SiO_2 then purified by flash chromatoghaphy.
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