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UNUSUAL α-AMINOACIDS FROM VINYLGLYCINE

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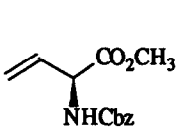
Summary : The easily available L-vinylglycine derivative **1** is used in the synthesis of unusual multifunctional α-aminoacids such as **2** and **3**.

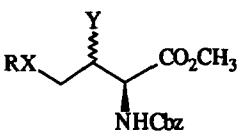
Unusual α-aminoacids like β-hydroxy α-aminoacids (1) or dehydroaminoacids (2) have recently received much attention not only as usefull synthons in the synthesis of natural products but also because of their biological properties alone or as part of peptides.

Vinylglycine has been widely used as the alkenic substrate in 1,3-dipolar cycloadditions of nitrile oxides to alkenes, especially in the synthesis of acivicin, an antitumor agent (3). It is a key intermediate in the synthesis of analogues of the mitomycin antitumor antibiotics (4) and has also been used in the syntheses of 3-chlorovinylglycine (5), of cis-substituted β-lactams (6) and of 2'-epi-distichonic acid A, an iron-chelating aminoacid derivative (7).

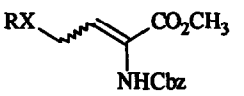
In the present communication, we report the use of the fully protected L-vinylglycine **1**, now easily available in large scale from L-methionine (8), as a starting material in the synthesis of some multifunctional α-aminoacids of type **2** and **3** :



1



2



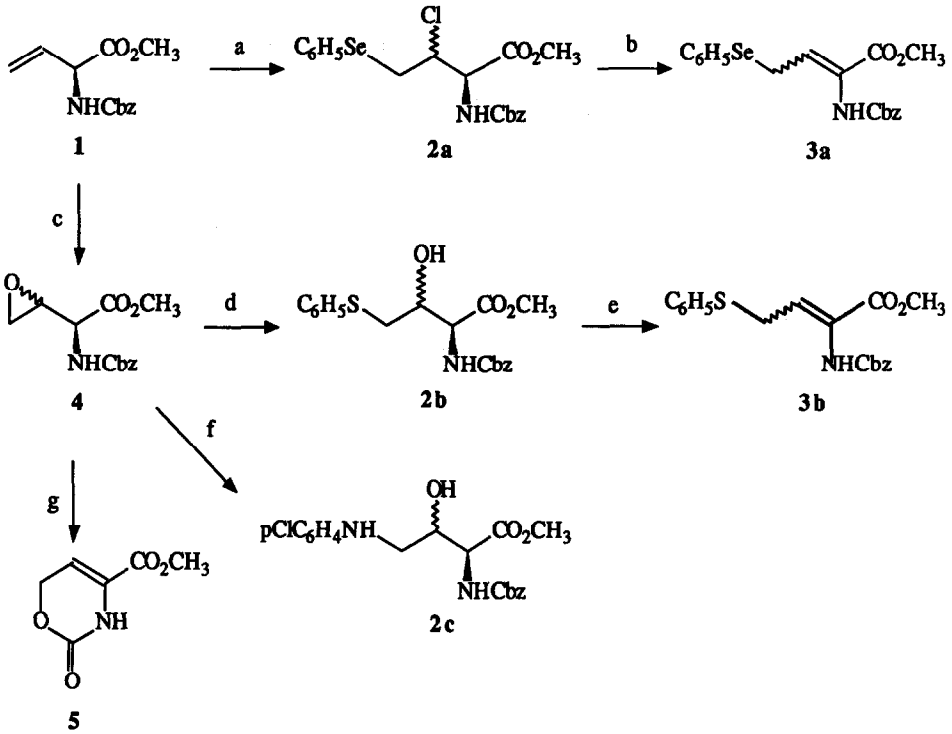
3

X=N, O, S, Se
Y=Cl, OH
Cbz=$CO_2CH_2C_6H_5$
R=aryl

The selenium-containing derivative **3a** was prepared by addition of phenylselenyl chloride on the double bond of **1** through a transient chlorinated derivative **2a** (5). Only the α,β-unsaturated derivative **3a** was obtained, in good yield.

The epoxides **4** were easily synthesized from **1** as a diastereomeric mixture via MCPBA oxidation (4) (1:4 ratio of erythro and threo epoxides).

Initial attempts to open the epoxides **4** according to the experimental method of Shaw and coll. failed (4), but regioselective attack of **4** by sodium thiophenoxide and by p-chloroaniline in methanol at room temperature could be achieved, resulting in clean formation of ring opened products **2b** and **2c** respectively.



a- C_6H_5SeCl : 1.1 eq., CH_3CN, 0°C-rt, 2h. b- DBU : 1.5 eq., $C_6H_5CH_3$, -20°C-rt, 15min, yield : 45% from 1. c- MCPBA : 5eq., CH_2Cl_2, rt, 40h, yield : 95%. d- C_6H_5SH : 2.5 eq., Na_2CO_3 : 1.5 eq., CH_3OH, rt, 12h, yield : 96%. e- MsCl : 2.5 eq., $N(C_2H_5)_3$: 4 eq., CH_2Cl_2, 0°C-rt, 4h then DBU : 3eq., $C_6H_5CH_3$, -60°,1h , yield : 95% from 2b. f- p-$ClC_6H_4NH_2$: 1eq., CH_3OH, rt, 8 days, yield : 44%. g- CH_3ONa : 1 eq., CH_3OH, 0°C, 1h yield : 9% or CH_3OH/Al_2O_3, $C_2H_5OC_2H_5$, rt, 1h (9) or p-ClC_6H_4OH : 2.5 eq., Na_2CO_3 : 1.5 eq., CH_3OH, 0°C-rt, 4h, yield : 45% or Na_2CO_3 : 1.5 eq., CH_3OH, 0°C-rt, 4h, yield : 25%.

Opening the epoxides with thiophenoxide occurred in high yield and allowed to carry on the sequence yielding the α,β-unsaturated derivative **3b** in a classical way.

p-Chloroaniline gave moderate yield of adduct probably because of the poor nucleophilicity of its nitrogen. However, as recently reported (7), the use of an aliphatic amine did not increase the yield. Furthermore, all attempts to open the mixture of epoxides **4** with oxygen nucleophiles (p-$ClC_6H_4O^-$, CH_3O^-) in various conditions (9) failed and led to the 2,3-dihydro-1,3-6H-oxazine **5** (4) and to benzyl alcohol instead of the desired β-hydroxy α-aminoacid derivative **2** (X=O and Y= OH).

This reaction probably involves abstraction of the α-proton, and formation of an allylic alkoxide which intramolecularly reacts with the carbamate protecting group (10).

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11- 1H NMR (250 MHz, $CDCl_3$, ppm vs TMS) :

3a : δ 7-7.5 (m, 10 H, Arom.) ; 6.67 (t, 1H, 8 Hz, -CH=) ; 5.85 (bs, 1H, NH) ; 5.03 (s, 2H, $CH_2C_6H_5$) ; 3.64 (s, 3H, CO_2CH_3) ; 3.54 (d, 2H, 8 Hz, $SeCH_2$).

4 (threo/erythro : 4/1) : δ 7.2-7.4 (m, 5H, Arom.) ; 6.7 (bd, 1H, NH) ; 5.10 (s, 2H, $CH_2C_6H_5$) ; 4.39 (m, 1H, CHN) ; 3.74 (s, 3H, CO_2CH_3) ; 3.2-3.4 (2m, 1H, $CHOCH_2$) ; 2.6-2.8 (2m, 2H, $CHOCH_2$).

2b : δ 7-7.5 (m, 10 H, Arom.) ; 5.5-5.8 (2bd, 1H, 9 Hz, NH) ; 5-5.1 (2s, 2H, $CH_2C_6H_5$) ; 4.46 (bd, 1H, 8 Hz, CHN) ; 3.9-4.2 (2bs, 1H, OH) ; 3.64 (s, 3H, CO_2CH_3) ; 2.6-3.2 (m, 3H, SCH_2, CHOH).

3b : δ 7.1-7.3 (m, 10 H, Arom.) ; 6.55 (t, 1H, 7.5 Hz, -CH=) ; 6.15 (bs, 1H, NH) ; 5.07 (s, 2H, $CH_2C_6H_5$) ; 3.67 (s, 3H, CO_2CH_3) ; 3.61 (d, 2H, 7.5 Hz, SCH_2).

2c : δ 7.37 (s, 5H, $C_6H_5CH_2$) ; 7.12 (d, 2H, 8.5 Hz, H arom. meta) ; 6.57 (d, 2H, 8.5 Hz, H arom. ortho) ; 5.6-5.9 (2bd, 1H, 8.5 Hz, NHCbz) ; 5.13-5.15 (2s, 2H, $CH_2C_6H_5$) ; 4.55 (d, 1H, 8.4 Hz, CHN) ; 4.32 (bt, 1H, 6.3 Hz, CHOH) ; 3.70, 3.76 (2s, 3H, CO_2CH_3) ; 3.21 (d, 2H, 6.3 Hz, CH_2N).

5 : δ 7.35 (bs, 1H, NH) ; 6.05 (dt, 1H, 3.7 Hz, 1.8 Hz, -CH=) ; 4.96 (d, 2H, 3.7 Hz, OCH_2) ; 3.85 (s, 3H, CO_2CH_3).

CIMS (NH_3) :

3a : 406 $(M+H)^+$; 423 $(M+NH_4)^+$; **4** : 266 $(M+H)^+$; 283 $(M+NH_4)^+$; **2b** : 376 $(M+H)^+$; 393 $(M+NH_4)^+$; 358 $(M-H_2O+H)^+$; **3b** : 358 $(M+H)^+$; 375 $(M+NH_4)^+$; **2c** : 393 $(M+H)^+$; **5** : 158 $(M+H)^+$; 175 $(M+NH_4)^+$.

Melting points :

2c : 133-134°C (diethyl ether) ; **5** : 122-123°C (diethyl ether/pentane).

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