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PREPARATION OF γ-OXO-α-AMINO ACIDS FROM SILYL ENOL ETHERS AND GLYCINE CATION EQUIVALENTS; A FACILE SYNTHESIS OF (±)-5-HYDROXY-4-OXONORVALINE (HON)

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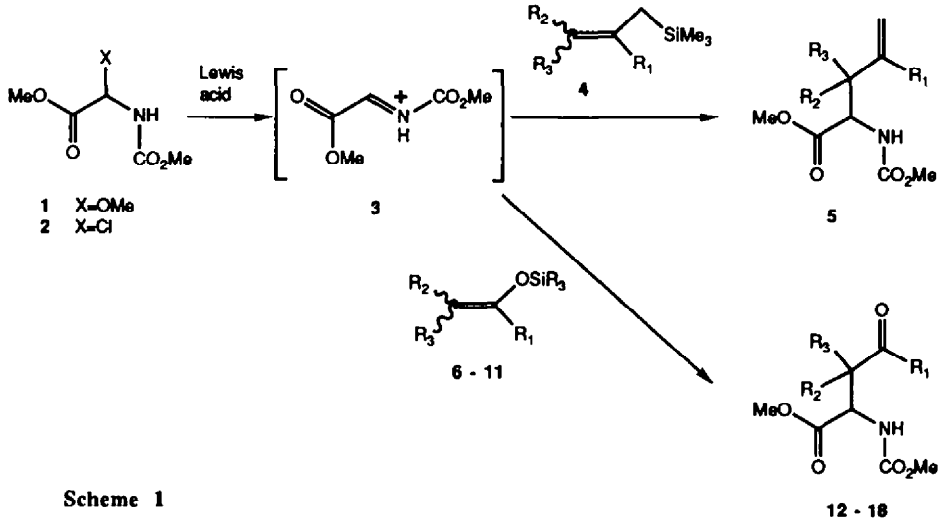
Summary: The synthesis of a series of *N*-methoxycarbonyl γ-oxo-α-amino acid methyl esters through Lewis acid-induced coupling of the corresponding chloroglycine derivative with different silyl enol ethers is described. The products can be easily converted into the free α-amino acids, as is illustrated for the synthesis of 5-hydroxy-4-oxonorvaline (HON), a natural product with antitubercular and antifungal properties.

INTRODUCTION

The synthesis of α-amino acids continues to attract considerable attention, because of the ever-increasing use of these compounds in many disciplines of the physical and life sciences.[1] A particularly appealing synthetic approach toward α-amino acids involves the use of the glycine cation **3** as intermediate.[2,3,4]

We recently reported the synthesis of a series of γ,δ-unsaturated *N*-protected α-amino acid methyl esters **5** through Lewis acid-induced coupling of different allylsilanes **4** with glycine cation equivalents **1** and **2** (see Scheme 1).[5] These results prompted us to investigate other π-nucleophiles in this reaction.



Scheme 1

We now wish to report our results on the facile synthesis of a series of *N*-protected γ-oxo-α-amino acid methyl esters **12-18** through Lewis acid-induced coupling of different silyl enol ethers **6-9** and ketene acetals **10** and **11** with chloroglycine derivative **2**. The utility of this procedure will be emphasized with the synthesis of the naturally occurring α-amino acid 5-hydroxy-4-oxonorvaline.

Silyl enol ethers have first been used successfully in amidoalkylation reactions by Shono and coworkers. [6] This methodology was recently extended to an optically active *N*-acyliminium intermediate by Wanner and coworkers.[7] Williams's group [8] has extensively investigated the use of a complex chiral analogue of **3** for the asymmetric synthesis of α-amino acids.

While our work was in progress, three articles appeared describing reactions of simple precursors like **1** and **2** with siloxy substituted olefins.[9-11] Steckhan and coworkers [9] described the coupling of an excess (4-6 equiv) of a silyl enol ether with a methoxyglycine derivative. Hartmann and Obrecht [10] published the coupling of 2-trimethylsiloxy-1,3-butadiene with protected bromoglycine. Steglich and coworkers [11] studied the coupling of silyl enol ethers with an *N*-acylimino acetate, obtained in situ from the corresponding bromoglycine by base induced elimination of HBr. In the present paper we compare our methodology with Steglich's procedure.

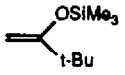
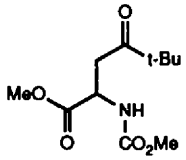
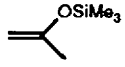
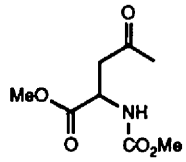
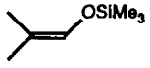
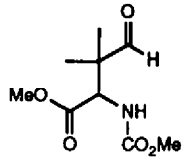
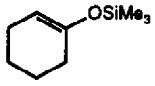
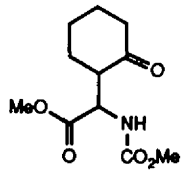
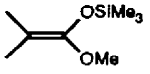
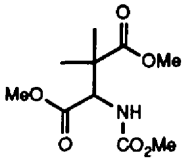
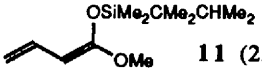
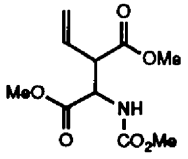
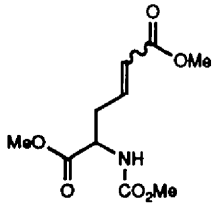
RESULTS AND DISCUSSION

The results are collected in Table 1. The silyl enol ethers **6-11** were either commercially available or prepared according to literature procedures (see Experimental). Generation of the intermediate **3** from the chloroprecursor **2** [12] was effected with 2 equiv of tin tetrachloride. In a typical experiment tin tetrachloride was added to a mixture of **2** and the silicon nucleophile in dichloromethane as solvent, at -78 °C. After stirring for 15 min at -78 °C, the reaction mixture was allowed to warm up to room temperature, at which temperature stirring was continued for a further 2-3 h. Yields based on **2** varied from moderate using the simple silyl enol ether **7** (entry 3), to excellent using the silyl enol ether **9** (entry 5). Higher yields were obtained when excess silyl enol ether was used in the reaction. Thus, when 1.1 equiv of **6** was used, the coupling product **12** was obtained in 67% (entry 2), whereas the yield rose to 96% when 2.0 equiv of **6** was employed (entry 1). This effect could also be observed in the reaction with the dimethylthexylsilyl ketene acetal **11** (entry 7, 8). No higher yields were obtained when titanium tetrachloride served as Lewis acid. When the methoxyglycine precursor **1** was used to generate the *N*-acyliminium ion intermediate **3**, using 4 equiv of boron trifluoride etherate, poor yields were obtained in reactions with silyl enol ethers. For instance with 1.1 equiv of **6**, **12** was formed in only 31% yield. These results correspond with our earlier findings for the reactions of **1** and **2** with allylsilanes. [5]

In those cases where stereoisomers were formed (entry 5, 7), little stereoselectivity was observed, and the product isomers could not be separated. The isomer ratio's were determined from the ^{1}H-NMR spectra by integration of the hydrogens located α or β to nitrogen. A 2 : 1 regioisomeric mixture was obtained from the reaction with dimethylthexylsilyl ketene acetal **11**, with a preference for the branched product **17** over the linear product **18**, which products could be easily separated by flash chromatography. Thus, the interesting vinyl substituted aspartic acid derivative **17** can be easily prepared by this method. It was recently reported [13] that an intermolecular amidoalkylation reaction of **11** with a less reactive *N*-acyliminium ion gave a 1 : 1 regioisomeric mixture of the branched and linear products.

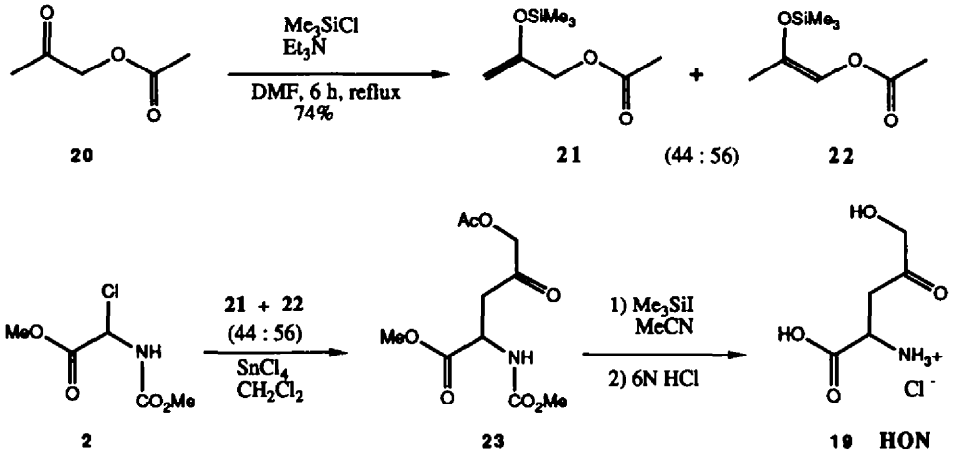
While our work was in progress, the article of Steglich and coworkers [11] appeared, describing the Lewis acid-induced coupling of silyl enol ethers with an *N*-acylimino acetate, which was obtained in situ from the corresponding bromoglycine by treatment with triethylamine. We wondered whether the addition of triethylamine to our chloroglycine derivative **2** would give better coupling results. We therefore performed some reactions according to the procedure of Steglich, with chloroglycine derivative **2**, triethylamine, tin tetrachloride, and silyl enol ether **6**. However, only poor yields of the coupling product **12** were obtained. Thus, we conclude that the best results in the reaction of **2** with silyl enol ethers are obtained by direct Lewis acid-induced *N*-acyliminium ion

Table 1

entry	silyl enol ether (equiv)		product (isolated yield based on **2**, isomer ratio)	
1		**6** (2.0)		**12** (96%)
2		**6** (1.1)		**12** (67%)
3		**7** (1.0)		**13** (46%)
4		**8** (1.2)		**14** (65%)
5		**9** (1.6)		**15** (96%) (30 : 70)
6		**10** (1.4)		**16** (89%)
7		**11** (2.0)	 **17** (50 : 50)	(56%) (67 : 33)  **18** (E : Z = 72 : 28)
8		**11** (1.1)		(30%, 67 : 33)

(3) formation, rather than an in situ formation of an *N*-acylimino acetate, using triethylamine. Apparently, the better leaving group ability of bromide with respect to chloride is a decisive factor.

A particularly interesting γ-oxo-α-amino acid is 5-hydroxy-4-oxonorvaline (HON) (**19**), discovered in Japan in 1958 in the culture broth of *Streptomyces akiyoshienis novo sp.*.[14] The structure of HON was determined by Miyake et al. in 1960, and was confirmed by synthesis starting from bromoacetone and diethyl *N*-acetamidomalonate.[15] HON possesses antitubercular [16] and antifungal properties.[17] Recently, a study of its biosynthesis was published.[18] Herewith, we present a short synthesis of HON, based upon the procedure described above (Scheme 2).



Scheme 2

The silyl enol ether **21**, required for the synthesis of HON, was to the best of our knowledge unknown in the literature. It was prepared according to the procedure of House et al. [19] Thus, heating inexpensive acetoxyacetone (**20**) with chlorotrimethylsilane and triethylamine in dimethylformamide for 6 h gave, after work up and distillation, a mixture of **21** and **22** in a 44 : 56 ratio with a total yield of 74%. Other methods [20] to prepare **21** from **20** were unsatisfactory. Because **21** could not be separated from **22** in a simple manner, the mixture was used as such for the coupling with **2**. The best yield of protected HON (**23**) was obtained, when 2 equiv of the mixture of **21** and **22** and 2 equiv of tin tetrachloride were used in dichloromethane as solvent (Scheme 2). In this manner, **23** could be isolated after flash chromatography in 58% yield, based on the amount of **21** used (47% based on **2**). The use of a larger excess of the silyl enol ether mixture (2.75 - 3 equiv) resulted in lower yields (24 - 27%) of **23**. Increasing the amount of tin tetrachloride to 3 equiv had no effect on the yield of **23**, but lowering the amount to 1.1 equiv resulted in a poor yield of 24%. With titanium tetrachloride as Lewis acid, similar results were obtained. Carbamate **23** could be easily converted into the free amine, by treatment with trimethylsilyl iodide in acetonitrile. In the final step the HCl-salt of HON (**19**) was obtained by treatment of the diester with 6N HCl. With ^{13}C-NMR and ^{1}H-NMR including decoupling techniques the structure of the amino acid salt was established unambiguously.

In conclusion, reactions of chloroglycine derivative **2** with various silyl enol ethers and ketene acetals in the presence of tin tetrachloride constitute a facile synthesis of protected γ-oxo-α-amino acids. The products can be easily converted into the free amino acids, as is shown for the synthesis of 5-hydroxy-4-oxonorvaline (HON).

EXPERIMENTAL

General information. All reactions were carried out in an inert atmosphere of dry nitrogen, unless otherwise described. Standard syringe techniques were applied for transfer of Lewis acids and dry solvents. Infrared spectra (IR) were obtained from $CHCl_3$ solutions, using a Perkin-Elmer 298 or Perkin-Elmer 1310 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined in $CDCl_3$ as solvent, unless indicated otherwise, using a JEOL PMX 60 (60 MHz), a Bruker AC 200 (200 MHz) or a Bruker WM 250 (250 MHz) spectrometer. ^{13}C-NMR spectra were recorded on a Bruker AC 200 or Bruker WM 250 instrument. Chemical shifts are given in ppm downfield from tetramethylsilane. Mass spectra were recorded on a Varian MAT 711 or a VG Micromass ZAB-2HF instrument. R_f values were obtained by using thin layer chromatography (TLC) on silica-gel-coated plastic sheets (Merck silica gel 60 F_{254}) with the indicated solvent (mixture). Chromatographic purification refers to flash chromatography with Merck silica gel 60 (230-400 mesh). Melting and boiling points are uncorrected. CH_2Cl_2 was distilled from P_2O_5 and kept under an atmosphere of dry nitrogen. $BF_3{\cdot}OEt_2$, $SnCl_4$ and $TiCl_4$ were distilled and stored under an atmosphere of dry nitrogen, $SnCl_4$ and $TiCl_4$ as a 1.2 M solution in CH_2Cl_2. 2-(Trimethylsiloxy)propene (**7**), 1-(trimethylsiloxy)cyclohexene (**9**), 1-methoxy-2-methyl-1-trimethylsiloxypropene (**10**) and acetoxyacetone (**20**) were purchased from Fluka. Iodotrimethylsilane was purchased from Aldrich.

General procedure for the coupling of 2 with silyl enol ethers. The silyl enol ether (1.0-2.0 equiv) was added at room temperature to a 0.2 - 0.5 M solution of moisture sensitive chloride **2** [2] in dry CH_2Cl_2 (**2** was weighed under nitrogen). The reaction mixture was cooled to -78 °C. Tin tetrachloride (2 equiv) was added slowly to the reaction mixture. After a further 15 min at -78 °C, the reaction mixture was allowed to warm up to room temperature and was stirred for a further 3 h. The reaction mixture was then carefully poured out into ice-cold saturated aq $NaHCO_3$. Tin salts were removed by filtration through a sintered glass funnel with the aid of Celite. The filter was rinsed with $CHCl_3$. The organic filtrate was washed with aq $NaHCO_3$ (2x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed.

Carbamate 12. According to the general procedure, starting from 284.6 mg (1.652 mmol) of **6** [19], 150.0 mg (0.826 mmol) of **2**, 4.0 mL CH_2Cl_2, and 1.38 mL (1.652 mmol; 1.2 M solution in CH_2Cl_2) of $SnCl_4$, there was obtained 193.5 mg (0.789 mmol, 96%) of **12**, after flash chromatography, R_f 0.38 (EtOAc : hexane = 60 : 40), as a crystalline compound, m.p. 39-42 °C. IR ($CHCl_3$): 3480-3300, 2995, 2950-2800, 1800-1650, 1500. ^{1}H-NMR (250 MHz): 5.67 (d, 1 H, *J* 7.8 Hz, NH), 4.53 (dt, 1 H, *J* 4, 8.7 Hz, CH-N), 3.69 (s, 3 H, CH_3O-C(O)-C), 3.65 (s, 3 H, CH_3O-C(O)-N), 3.25 (dd, 1 H, *J* 4, 18.3 Hz, -CH_2-C(O)), 3.00 (dd, 1 H, *J* 4, 18.3 Hz, -CH_2-C(O)), 1.10 (s, 9 H, ($(CH_3)_3$C-). ^{13}C-NMR (50 MHz): 214.2 (C-C(O)-C), 171.6 (CH_3O-C(O)C), 156.7(CH_3O-C(O)-N), 52.5, 52.3 (CH_3O-C(O)-C, CH_3O-C(O)-N), 50.0 (CH-N), 43.9 (-CH_2-C(O)), 39.0 ($(CH_3)_3$C), 26.1 ($(CH_3)_3$C). Exact mass 245.1261 (Calcd. for $C_{11}H_{19}NO_5$ 245.1263).

Carbamate 13. According to the general procedure, starting from 1.00 mL (546.0 mg, 4.192 mmol, 70% solution) of **7**, 745.0 mg (4.103 mmol) of **2**, 10.0 mL CH_2Cl_2, and 6.84 mL (8.208 mmol; 1.2 M solution in CH_2Cl_2) of $SnCl_4$, there was obtained 383.4 mg (1.887 mmol, 46%) of **13**, after flash chromatography, R_f 0.20 (EtOAc : hexane = 40 : 60), as a yellow oil. IR ($CHCl_3$): 3470, 3000, 2980, 1800-1650, 1500. ^{1}H-NMR (200 MHz): 5.69 (d, 1 H, *J* 7.7 Hz, NH), 4.52 (dt, 1 H, *J* 4.3, 8.6 Hz, CH-N), 3.71 (s, 3 H, CH_3O-C(O)-C), 3.66 (s, 3 H, CH_3O-C(O)-N), 3.18 (dd, 1 H, *J* 4.3, 18.3 Hz, -CH_2-C(O)), 2.95 (dd, 1 H, *J* 4.3, 18.3 Hz, CH_2-C(O)), 2.14 (s, 3 H, CH_3-C(O)). ^{13}C-NMR (50 MHz): 206.1 (C-C(O)-C), 171.4 (CH_3O-C(O)-C), 156.0 (CH_3O-C(O)-N), 60.0 (CH-N), 52.5, 52.2 (CH_3O-C(O)-C, CH_3O-C(O)-N), 45.0 (-CH_2-C(O)), 29.6 (CH_3-C(O)).

Carbamate 14. According to the general procedure, starting from 525.8 mg (3.644 mmol) of **8** [20a], 551.4

mg (3.037 mmol) of **2**, 7.0 mL CH_2Cl_2, and 5.06 mL (6.075 mmol; 1.2 M solution in CH_2Cl_2) of $SnCl_4$, there was obtained 430.7 mg (1.983 mmol, 65%) of **14**, after flash chromatography, R_f 0.20 (EtOAc : hexane = 45 : 55), as a crystalline compound, m.p. 74-78 °C. IR ($CHCl_3$): 3435, 3000-2890, 1800-1650, 1505. ^{1}H-NMR (250 MHz): 9.55 (s, 1 H, HC(O)), 5.38 (d, 1 H, *J* 8.9 Hz, NH), 4.67 (d, 1 H, *J* 9.5, CH-N), 3.70 (s, 3 H, CH_3O-C(O)-C), 3.68 (s, 3 H, CH_3O-C(O)-N), 1.11 (s, 3 H, CH_3-C), 1.03 (s, 3 H, CH_3-C). ^{13}C-NMR (62 MHz): 201.8 (HC(O)), 170.5 (CH_3O-C(O)-C), 156.8 (CH_3O-C(O)-N), 58.0 (CH-N), 52.5, 52.3 (CH_3O-C(O)-C, CH_3O-C(O)-N), 49.6 ($(CH_3)_2C$), 19.0 (CH_3-C), 17.8 (CH_3-C).

Carbamate 15. According to the general procedure, starting from 6.80 g (39.92 mmol) of **9**, 4.48 g (24.67 mmol) of **2**, 50.0 mL CH_2Cl_2, and 41.1 mL (49.32 mmol; 1.2 M solution in CH_2Cl_2) of $SnCl_4$, there was obtained 5.79 g (23.80 mmol, 96%) of **15**, after flash chromatography, R_f 0.50 (EtOAc : hexane = 40 : 60), as a yellow oil, as a mixture of isomers (30 : 70). IR ($CHCl_3$): 3440, 3000, 2940, 2860, 1725, 1510. ^{1}H-NMR (250 MHz) : 5.65 (d, 1 H, *J* 8.6 Hz, NH, minor isomer), 5.47 (d, 1 H, *J* 10.0 Hz, NH, major isomer), 4.26-4.17 (m, 1 H, CH-N), 3.54-3.50 (m, 6 H, CH_3O-C(O)-C, CH_3O-C(O)-N), 3.15-3.09 (m, 1 H, CH-C(O), major isomer), 2.70-2.64 (m, 1 H, CH-C(O), minor isomer), 2.22-2.10 (m, 2 H, CH_2-C(O)), 1.99-1.39 (m, 6 H, CH-CH_2-CH_2-CH_2-). ^{13}C-NMR (50 MHz): 211.0 (CH_2-C(O)-CH), 171.3 (CH_3O-C(O)-C), 157.2 (CH_3O-C(O)-N), 53.8, 53.6, 53.4, 52.5, 52.1, 51.9, 51.8 (two isomers, CH_3O-C(O)-C, CH_3O-C(O)-N, CH-N, CH_2-CH-C(O)), 41.4 (C(O)-CH_2-CH_2, major isomer), 41.3 (C(O)-CH_2-CH_2, minor isomer), 30.2 (CH-CH_2-CH_2), 26.8 (CH-CH_2-CH_2-CH_2, major isomer), 26.6 (CH-CH_2-CH_2-CH_2, minor isomer), 24.5 (CH_2-CH_2-CH_2-C(O), major isomer), 24.3 (CH_2-CH_2-CH_2-C(O), minor isomer). Exact mass 243.1101 (calcd. for $C_{11}H_{17}NO_5$ 243.1106).

Carbamate 16. According to the general procedure, starting from 2.50 mL (2.04 g, 11.718 mmol, 95%) of **10**, 1.53 g (8.426 mmol) of **2**, 20.0 mL CH_2Cl_2, and 14.04 mL (16.852 mmol; 1.2 M solution in CH_2Cl_2) of $SnCl_4$, there was obtained 1.85 g (7.470 mmol, 89%) of **16**, after flash chromatography, R_f 0.35 (EtOAc : hexane = 40 : 60), as a crystalline compound, m.p. 41-42 °C. IR ($CHCl_3$): 3440, 2980, 2950, 1725, 1500. ^{1}H-NMR (250 MHz): 5.58 (d, 1 H, *J* 9.1 Hz, NH), 4.56 (d, 1 H, *J* 9.8 Hz, CH-N), 3.66 (s, 6 H, CH_3O-C(O)-C, CH_3O-C(O)-C), 3.65 (s, 3 H, CH_3O-C(O)-N), 1.24 (s, 3 H, CH_3-C), 1.14 (s, 3 H, CH_3-C). ^{13}C NMR (50 MHz): 175.7 (CH_3O-C(O)-C), 170.8 (CH_3O-C(O)-CH), 157.0 (CH_3O-C(O)-N), 59.9 (CH-N), 52.4, 52.3, 52.1 (CH_3O-C(O)-C, CH_3O-C(O)-C, CH_3O-C(O)-N), 45.4 (C(O)-C-CH), 22.9, 21.6 (CH_3-C, CH_3-C). Mass spectrum : $M^{+\bullet}$- (CH_3-O-C(O)) = 247.

Carbamates 17 and 18. According to the general procedure, starting from 1101.2 mg (4.294 mmol) of **11** [13], 390.0 mg (2.147 mmol) of **2**, 8.0 mL CH_2Cl_2, and 3.58 mL (4.294 mmol; 1.2 M solution in CH_2Cl_2) of $SnCl_4$, there was obtained 297.4 mg (1.213 mmol, 56%) of a 67 : 33 mixture of **17** and **18**, which could be separated by flash chromatography (CH_2Cl_2 : acetone = 83 : 17). **17** : R_f 0.60 (CH_2Cl_2 : acetone = 83 : 17), as a mixture of isomers (50 : 50). IR ($CHCl_3$): 3435, 3060-3000, 3000-2950, 1800-1660, 1505. ^{1}H-NMR (200 MHz): 5.90-5.72 (m, 1 H, CH=CH_2), 5.68 (d, 1 H, *J* 9.2 Hz, NH), 5.30-5.20 (m, 2 H, CH=CH_2), 4.70 (d, 1 H, *J* 9.7 Hz, CH-N, one isomer), 4.68 (d, 1 H, *J* 9.7 Hz, CH-N, one isomer), 3.78-3.52 (m, 10 H, CH_3O-C(O)-C, CH_3O-C(O)-C, CH_3O-C(O)-N, -CH-CH=CH_2). ^{13}C-NMR (50 MHz): 171.8, 170.7 (CH_3O-C(O)-C, CH_3O-C(O)-C), 156.8 (CH_3O-C(O)-N), 130.8 (-CH=CH_2), 120.4 (-CH=CH_2), 55.8 (CH-N), 52.6, 52.5, 52.3 (CH_3O-C(O)-C, CH_3O-C(O)-C, CH_3O-C(O)-C), 51.1 (=C-CH). **18** : R_f 0.50 (CH_2Cl_2 : acetone = 83 : 17), as a mixture of E - Z isomers (72 : 28). IR ($CHCl_3$): 3600-3300, 3080-3000, 2995-2840, 1800-1660, 1505. ^{1}H-NMR (200 MHz): 6.87-6.71 (m, 1 H, -CH=CH-C(O)-OCH_3, E isomer), 6.41-6.21 (m, 1 H, CH=CH-C(O)-OCH_3 , Z isomer), 5.92-5.28 (m, 1 H, -CH=CH-C(O)-OCH_3, E and Z isomers), 5.45-5.17 (m, 1 H, NH, E and Z isomers), 4.52-4.20 (m, 1 H, CH-N, E and Z isomers), 3.73-3.64 (m, 9 H, CH_3O-C(O)-C, CH_3O-C(O)-C, CH_3O-C(O)-N, E and Z isomers), 2.62-2.08 (m, 2 H, -CH_2-CH=, E and Z isomers).

Silyl enol ethers 21 and 22. To a solution of 3.26 g (3.81 mL, 30.0 mmol) of chlorotrimethylsilane and 6.07 g (8.36 mL, 60.0 mmol) of triethylamine in 10.0 mL of dimethylformamide, was added 2.90 g (2.70 mL, 25.0 mmol) of acetoxyacetone. The resulting mixture, from which some pale yellow solid separated immediately and more separated during the reaction (presumably triethylamine hydrochloride), was refluxed with stirring for 6 h. After cooling, the reaction mixture was diluted with pentane (100 mL), poured out into saturated aq. $NaHCO_3$, and extracted with pentane (3x50 mL). The combined organic extracts were washed with saturated aq $NaHCO_3$ (2x), dried (K_2CO_3) and evaporated in vacuo. Purification by destillation (b.p. 68-70 °C, 12 mm Hg), yielded 3.47 g (18.5 mmol, 74%) of a mixture (44 : 56) of **21** and **22**. IR ($CHCl_3$): 3110, 3040-3010, 2955, 1735, 1380, 1370, 1280-1180, 970, 895, 840. ^{1}H-NMR (60 MHz): 6.8-6.7 (m, 1 H, =C<u>H</u>-O-C(O)-CH_3, **22**, Z-isomer), 6.5-6.4 (m, 1 H, =C<u>H</u>-O-C(O)-CH_3, **22**, E-isomer), 4.3 (s, 2 H, -C<u>H</u>$_2$-O-C(O)-CH_3, **21**), 4.3-4.2 (m, 2 H, <u>H</u>$_2$C=, **21**), 2.1 (s, 3 H, -O-C(O)-C<u>H</u>$_3$, **21** and **22**), 1.8 (s, 3 H, C<u>H</u>$_3$-C($OSiMe_3$)=, **22**, Z-isomer), 1.7 (s, 3 H, C<u>H</u>$_3$-C($OSiMe_3$)=, **22**, E-isomer), 0.3 (s, 9 H, OSi(C<u>H</u>$_3$)$_3$, **21** and **22**).

Carbamate 23. According to the general procedure, starting from 1227.0 mg (6.517 mmol) of a mixture of **21** and **22** (44 : 56), 591.7 mg (3.259 mmol) of **2**, 4.0 mL CH_2Cl_2, and 5.43 mL (6.518 mmol; 1.2 M solution in CH_2Cl_2) of $SnCl_4$, there was obtained 397.6 mg (1.522 mmol, 47%) of **23**, after flash chromatography, R_f 0.25 (EtOAc : hexane = 66 : 33), as a crystalline compound, m.p. 59-60 °C. IR ($CHCl_3$): 3500-3380, 3010-2910, 1800-1670, 1230. ^{1}H-NMR (250 MHz): 5.67 (d, 1 H, *J* 7.7 Hz, N<u>H</u>), 4.61 (s, 2 H, O-C<u>H</u>$_2$-C(O)-), 4.56 (q, 1 H, *J* 4 Hz, C<u>H</u>-N), 3.70 (s, 3 H, C<u>H</u>$_3$O-C(O)-C), 3.64 (s, 3 H, C<u>H</u>$_3$O-C(O)-N), 3.04 (dq, 2 H, *J* 4.4, 18 Hz, AB part of ABXY system, C(O)-C<u>H</u>$_2$-CH), 2.12 (s, 3 H, C<u>H</u>$_3$-C(O)-O). ^{13}C-NMR (62 MHz): 202.0 (<u>C</u>(O)), 171.0 (CH$_3$O-<u>C</u>(O)-C), 169.9 (CH$_3$-<u>C</u>(O)-O), 156.8 (CH$_3$O-<u>C</u>(O)-N), 67.8 (CH$_3$-C(O)-O-<u>C</u>H$_2$), 52.7, 52.4 (<u>C</u>H$_3$O, <u>C</u>H$_3$O), 49.6 (<u>C</u>H-N), 40.8 (-C(O)-<u>C</u>H$_2$-CH), 20.3 (<u>C</u>H$_3$-C(O)-O). Mass spectrum : $M^{+\bullet}$- (CH$_3$-O-C(O)) = 202.

(±)-5-Hydroxy-4-oxonorvaline (19). To a solution of 1153.2 mg (4.415 mmol) of **23** in 15.0 mL of acetonitrile was added at room temperature under an atmosphere of dry nitrogen, 1.89 g (1.31 mL, 8.829 mmol) of iodotrimethylsilane. After being stirred for 1 h at 50-55 °C, the reaction mixture was poured out into 5% aq $NaHSO_4$ and washed with CH_2Cl_2 (3x30 mL). The water layer was made basic with K_2CO_3 and extracted with CH_2Cl_2 (4x30 mL). The combined organic fractions containing the free amine were dried (K_2CO_3) and concentrated in vacuo, to yield 466.5 mg (2.296 mmol, 52%) of the 5-acetoxy-4-oxonorvaline methyl ester. IR ($CHCl_3$): 3800-3300, 3020-2950, 1740, 1235. ^{1}H-NMR (60 MHz): 4.7 (s, 2 H, -O-C<u>H</u>$_2$-C(O)-), 4.1-3.8 (m, 1 H, N-C<u>H</u>), 3.7 (s, 3 H, C<u>H</u>$_3$O-C(O)-C), 3.0-2.8 (m, 2 H, -C<u>H</u>$_2$-CH), 2.3-2.0 (m, 5 H, N<u>H</u>$_2$, -C(O)-C<u>H</u>$_3$).
A solution of 466.5 mg (2.296 mmol) of 5-acetoxy-4-oxonorvaline methyl ester in 20.0 mL 6N HCl (aq) was stirred at 40-45 °C for 5 days. The mixture was evaporated in vacuo to yield a dark oil. This residue was decolourised by addition of 10.0 mL of distilled water and 50 mg of activated charcoal. The mixture was then filtered through a sintered glass funnel and evaporated in vacuo to yield 354.9 mg (1.933 mmol, 84%) of (±)-5-hydroxy-4-oxonorvaline (**19**) as a colourless oil, which could be crystallized by the addition of acetone. IR (KBr): 3700-3000, 2920, 1625. ^{1}H-NMR (250 MHz, D_2O): 4.40 (t, 1 H, *J* 5.5 Hz, C<u>H</u>-N), 4.34 (s, 2 H, HO-C<u>H</u>$_2$-C(O)-), 3.22 (d, 2 H, *J* 5 Hz, -C(O)-C<u>H</u>$_2$-CH). ^{1}H-NMR (250 MHz, 100% d_6-DMSO): 9.00-8.35 (br m, 5 H, N<u>H</u>$_3$, <u>H</u>O-C(O), <u>H</u>O-), 4.27-4.16 (m, 1 H, C<u>H</u>-N), 4.09 (s, 2 H, HO-C<u>H</u>$_2$-C(O)-), 3.13 (2xdd, 2 H, *J* 5.5, 18.5 Hz, C(O)-C<u>H</u>$_2$-CH, AB part of ABX system). Double resonance technique: irradiation of N<u>H</u>$_3$, <u>H</u>O-C(O), <u>H</u>O- (9.00-8.35 ppm): ^{1}H-NMR (250 MHz, 100% d_6-DMSO): 4.20 (t, 1 H, *J* 5.5 Hz, C<u>H</u>-N), 4.09 (s, 2 H, HO-C<u>H</u>$_2$-C(O)-), 3.13 (2xdd, 2 H, *J* 5.5, 18.5 Hz, C(O)-C<u>H</u>$_2$-CH, AB part of ABX system). irradiation of N-C<u>H</u> (4.27-4.16 ppm): ^{1}H-NMR (250 MHz, 100% d_6-DMSO): 9.00-8.35 (br m, 5 H, N<u>H</u>$_3$, <u>H</u>O-C(O), <u>H</u>O-), 4.06 (s, 2 H, HO-C<u>H</u>$_2$-C(O)-), 3.13 (q, 2 H, *J* 18.5 Hz, C(O)-C<u>H</u>$_2$-CH, AB system). ^{13}C-NMR (50 MHz, D_2O): 204.6 (<u>C</u>(O)), 172.8 (HO-<u>C</u>(O)-C), 68.8 (HO-<u>C</u>H$_2$-C(O)-), 50.1 (<u>C</u>H-N), 39.4 (C(O)-<u>C</u>H$_2$-CH).

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