Studies on Hydroxy Amino Acids. VI. Formation of the Oxazoline Derivatives from *N*-Acyl-β-hydroxy Amino Acid Peptides[1]

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Oxazoline derivatives were mainly obtained from the *O*-tosyl-*N*-acyl-β-hydroxy amino acid peptides by β-elimination reaction. Dehydroalanine or hydantoin derivatives were isolated when the urethane type acyl groups were used.

It was found in a study on the β-elimination reaction of the β-hydroxy amino acid derivatives that only oxazoline derivative (**3**) was obtained from *N*-(benzyloxycarbonyl)-glycyl-(or phenylalanyl-)-L-threonylglycine benzyl ester, *via* the corresponding *O*-tosylated intermediate.[2]

We have carried out further application of the β-elimination reaction to the *N*-acylseryl- or *N*-acylthreonyl peptide (Scheme 1).

Several acyl groups, benzoyl, phenylacetyl, benzyloxycarbonyl, *t*-butoxycarbonyl, *N*-(benzyloxycarbonyl)-glycyl, and *N*-(benzyloxycarbonyl)-D-phenylglycyl, were used as the *N*-acyl group of the β-hydroxy amino acid or peptide derivatives.

O-tosyl derivatives (**2**) were prepared by treatment of the *N*-acyl-β-hydroxy amino acid derivatives (**1**) and tosyl chloride in a pyridine solution at 0 °C. The yield and analytical data of *N*-acyl-β-hydroxy amino acid peptides (**1**) and *O*-tosylated peptides (**2**) are summarized in Tables 1 and 2, respectively.

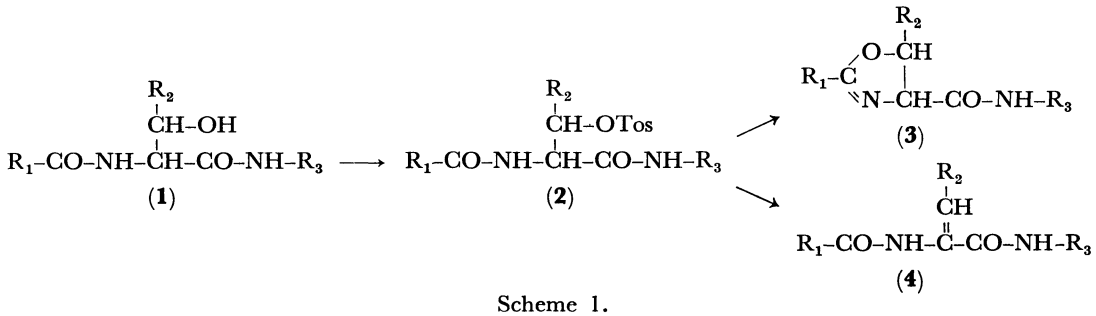
The detosylation reaction was carried out in a solution of tetrahydrofuran with triethylamine at 70 °C. The results are summarized in Tables 3 and 4. The structure of the products was confirmed by NMR spectra.

From the results of β-elimination reaction *O*-tosyl-*N*-acyl-β-hydroxy amino acid derivatives (**2**), we see that the resulting main products are oxazoline derivatives (**3**) but not dehydroalanine (**4**) or aziridine derivatives.

Table 1. Analytical data and yield of *N*-acyl-β-hydroxy amino acid derivatives (**1**)

Compd **1**	R_1	R_2CO	R_3	Yield(%)	Mp (°C)	$[\alpha]_D^{23}$ (*c* 1.0, DMF)	Found (Calcd) C%	H%	N%
a	CH_3	C_6H_5CO	Gly–OEt	95.1	128—130	+27.4	58.30 (58.43	6.67 6.54	9.11 9.09)
b	CH_3	$C_6H_5CH_2CO$	Gly–OEt	80.0	151—151.5	+7.8	59.85 (59.61	6.91 6.88	8.79 8.69)
c	CH_3	$C_6H_5CH_2CO$	Gly–OBzl	78.0	154—156	+8.5	65.74 (65.61	6.62 6.29	7.49 7.29)
d	CH_3	Z–D-Phg	OEt	87.1	141.5—142.5	−69.0	63.90 (63.75	6.28 6.32	6.93 6.76)
e	CH_3	Z–D-Phg	NH_2	77.1	223—224	−24.2	62.66 (62.32	5.95 6.02	10.82 10.90)
f	CH_3	Z–D-Phg	$NHCH_3$	66.0	224—225	−28.2	63.26 (63.14	6.38 6.31	10.17 10.52)
g	CH_3	Z–D-Phg	Gly–OBzl	70.5	175—177	−25.1	65.04 (65.28	5.75 5.86	7.78 7.88)
h	H	Z–D-Phg	OMe	81.6	171—172	−41.3	62.42 (62.16	5.87 5.74	7.32 7.25)
i	H	Z–D-Phg	NH_2	68.7	191—193	−10.8	61.34 (61.44	6.02 5.70	11.55 11.32)
j	H	Z–D-Phg	$NHCH_3$	61.7	212.5—213	−35.9	62.58 (62.32	5.87 6.02	10.64 10.90)
k	H	Z–D-Phe	OMe	88.0	146—147	+15.1	63.12 (62.99	6.13 6.04	6.98 7.00)
l	H	Z–D-Phe	$NHCH_3$	82.8	187—188	+15.0	63.37 (63.14	6.28 6.31	10.36 10.52)
m	CH_3	Z	Gly–OEt	76.8	110—111	+12.6	56.63 (56.79	6.32 6.55	8.41 8.28)
n	CH_3	Boc	Gly–OEt	81.3	86—87	−0.8	51.19 (51.30	7.99 7.95	9.42 9.21)
o	H	Z	Gly–OEt	92.5	97—98	+2.7	55.62 (55.55	6.37 6.22	8.59 8.64)
p	H	Boc	Gly–OBzl	89.0	81—82	−4.0	57.99 (57.94	6.81 6.87	7.90 7.95)

Z: benzyloxycarbonyl, Boc: *t*-butoxycarbonyl, Gly: glycine, Phg: phenylglycine, Me: methyl, Et: ethyl, Bzl: benzyl.



Scheme 1.

TABLE 2. ANALYTICAL DATA AND YIELD OF *O*-TOSYL-*N*-ACYL-*β*-HYDROXY AMINO ACID DERIVATIVES (**2**)

Compd **2**	Yield (%)	Mp (°C)	$[\alpha]_D^{23}$ (*c* 1.0, DMF)	Found (Calcd) C%	H%	N%	S%
a	94.0	105—106	+27.1	56.64 (57.13	5.62 5.67	5.92 6.06	6.55 6.93)
b	89.4	107—107.5	+18.9[a]	57.43 (57.97	5.95 5.92	5.84 5.88	6.71 6.73)
c	77.8	118.5—119.0	+23.7	62.43 (62.44	5.45 5.61	5.13 5.20	5.91 5.95)
e	39.4	135—136	+1.3	60.03 (60.10	5.22 5.42	7.91 7.79	5.96 5.94)
f	69.9	151—152	+0.7	60.49 (60.74	5.74 5.64	7.80 7.59	5.83 5.79)
g	90.0	96—97.5	+8.1	62.83 (62.87	5.40 5.42	6.12 6.11	4.48 4.66)
i	75.2	124—125	+1.6	59.27 (59.41	5.36 5.18	8.05 8.00	6.31 6.10)
j	80.0	139—139.5	+0.1	60.29 (60.10	5.44 5.42	7.80 7.79	6.02 5.94)
l	87.8	115—116	−71.6	60.63 (60.74	5.72 5.64	7.58 7.59	5.91 5.79)
m	90.0	93.5—94.0	+26.5	56.03 (56.08	5.73 5.73	5.69 5.69	6.30 6.51)
n	83.1	b)	+16.4[c]	52.32 (52.39	6.51 6.60	6.02 6.11	6.98 6.99)
o	77.8	97—98	+4.0	55.13 (55.22	5.62 5.48	5.90 5.85	6.83 6.70)
p	84.6	96—97[d]	+1.0	56.97 (56.90	5.91 5.97	5.65 5.53	6.45 6.33)

a) *c* 0.2, MeOH. b) Oil. c) *c* 1.2, DMF. d) Decomposition.

TABLE 3. REACTION PRODUCTS BY THE *β*-ELIMINATION REACTION OF THE *O*-TOSYLATED HYDROXY AMINO ACID DERIVATIVES (**2**)

Exp. No.	R_1	R_2	R_3	Yield (%) **3**	**4**	**5**
1	Ph–	$-CH_3$	$-CH_2-COOEt$	79.6	8.1	—
2	Ph–CH_2–	$-CH_3$	$-CH_2-COOEt$	80.3[a]	—	—
3	Ph–CH_2–	$-CH_3$	$-CH_2-COOBzl$	82.0[a]	—	—
4	Z–NH–CH_2–	$-CH_3$	$-CH_2-COOBzl$	80.0	—	—
5	Z–NH–CH(Ph)–	$-CH_3$	–H	70.7	—	—
6	Z–NH–CH(Ph)–	$-CH_3$	$-CH_3$	38.6	—	—
7	Z–NH–CH(Ph)–	$-CH_3$	$-CH_2-COOBzl$	70.4	26.7	—
8	Z–NH–CH(Ph)–	–H	–H	43.7	—	—
9	Z–NH–CH(Ph)–	–H	$-CH_3$	63.8	—	—
10	Z–NH–CH(CH_2–Ph)–	–H	$-CH_3$	65.4	—	—
11	Ph–CH_2–O–	$-CH_3$	$-CH_2-COOEt$	—	48.0	50.5
12	*t*-Bu–O–	$-CH_3$	$-CH_2-COOEt$	—	80.0	b)
13	Ph–CH_2–O–	–H	$-CH_2-COOEt$	—	52.0	38.6[c]
14	*t*-Bu–O–	–H	$-CH_2-COOBzl$	—	73.2	—

Ph: phenyl; Z: benzyloxycarbonyl; *t*-Bu: *t*-butyl; Et: ethyl; Bzl: benzyl. a) Small amounts of D-threonine derivative isolated. b) Trace amounts of **5**-11 isolated. c) **5**-13[4] not isolated by Photaki.

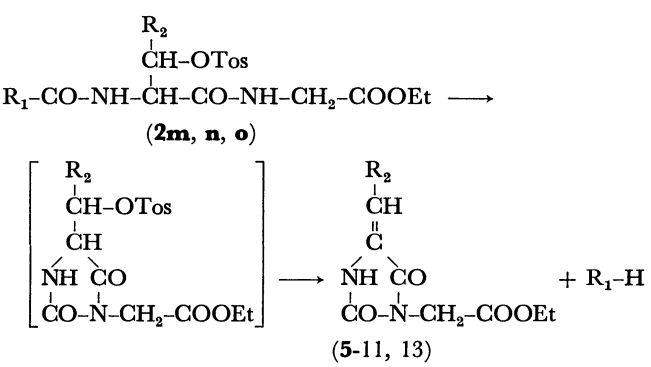
Table 4. Analytical data of the β-elimination reaction products (**3**, **4**, **5**)

Products	Mp(°C)	$[\alpha]_D^{23}$ (*c* 1.0, DMF)	Found (Calcd) C%	H%	N%
3-1	100—102	−20.6	61.78 (62.05	6.19 6.25	9.56 9.65)
3-2	88.5—89.0	−8.0[a]	63.41 (63.14	6.63 6.62	9.22 9.21)
3-3	94—94.5	−16.2[b]	68.87 (68.83	6.03 6.05	7.60 7.65)
3-5	144—145	+22.4	65.43 (65.38	5.68 5.76	11.28 11.44)
3-6	129—130	+25.5	65.87 (66.12	6.13 6.08	11.26 11.02)
3-7	c)	+3.0	67.43 (67.56	5.70 5.67	8.11 8.15)
3-8	157—158	+26.9	64.24 (64.58	5.47 5.42	11.89 11.89)
3-9	140—141	+67.7	65.45 (65.38	5.84 5.76	11.48 11.44)
3-10	114—115	+82.6	66.21 (66.12	6.06 6.08	11.02 11.02)
4-1	147—149	—	61.62 (62.05	6.23 6.25	9.60 9.65)
4-7	77—80	−21.7	67.12 (67.56	5.64 5.67	8.09 8.15)
4-11	109—110	—	59.65 (59.99	6.24 6.29	8.70 8.75)
4-12	93—93.5	—	54.69 (54.53	7.84 7.75	9.99 9.78)
4-13	81—82	—	58.69 (58.81	5.88 5.92	9.07 9.15)
4-14	103.5—104.5	—	61.11 (61.06	6.59 6.63	8.37 8.38)
5-11	155—155.5	—	50.86 (50.94	5.63 5.70	13.17 13.20)
5-13	104—105	—	48.39 (48.48	4.92 5.09	14.12 14.14)

a) *c* 0.2, MeOH. b) *c* 0.7, AcOEt. c) Oily product.

Z-Gly-Ser-Gly-OEt is an exceptional example to produce the dehydroalanine derivative (**4**) as the main product.[2]

In the case of urethane type acyl derivatives, however, both dehydroalanine (**4**) and hydantoin derivatives (**5**) were isolated from the *N*-benzyloxycarbonyl peptide derivatives, only the former being obtained from the *t*-butoxycarbonyl peptide derivatives (Scheme 2).



R_1: $C_6H_5CH_2O$- or $(CH_3)_3C$-O-, R_2: CH_3- or H-

Scheme 2.

Concerning the hydantoin formation, Dekker *et al.* reported[3] that compound (**5**) is produced when the *N*-[α-(benzyloxycarbonylamino)acyl]glycine ester is treated with methanolic ammonia at room temperature. However, we detected no aziridine derivatives.

Experimental

All the melting points are uncorrected. The NMR spectra were obtained with a Hitachi R-20 B High Resolution NMR Spectrometer, the chemical shifts being given from TMS as the internal reference. The purity of the compounds was confirmed by thin layer chromatography on silica gel. Hydroxy amino acid peptides were prepared by use of *N*,*N*′-dicyclohexylcarbodiimide (DCC). *N*-hydroxybenzotriazole (HOBt) or *N*-hydroxysuccinimide was employed in order to avoid the racemization of *N*-acyl-β-hydroxy amino acid during the course of coupling.

Synthesis of N-*Acyl-β-hydroxy Amino Acid Peptide Derivatives (**1**). Phenylacetyl-*L*-Thr-Gly-OEt (**1b**)*: All the dipeptide derivatives were synthesized as follows. Phenylacetyl-L-Thr-OH (23.7 g, 0.1 mol) was treated with DCC (22.7 g, 0.11 mol), H-Gly-OEt (from the hydrochloride 15.3 g, 0.11 mol), HOBt (16.2 g, 0.12 mol) in DMF (100 ml) and dichloromethane (100 ml) at −10 °C. After the reaction mixture had been allowed to stand overnight in a refrigerator, acetic acid (2 ml) was added and the mixture was stirred for 15 min. The *N*,*N*′-dicyclohexylurea produced was filtered off, and the filtrate was washed successively with 1 M sodium hydrogencarbonate, 1 M hydrochloric acid and water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. **1b** was obtained from ethyl acetate–ether–hexane as crystals. The results are summarized in Table 1.

*Z-D-Phg-L-Thr-NHCH$_3$ (**1f**)*: Methylamidation was carried out as follows. A solution of 30% methylamine (45 ml) in methanol was added to a solution of **1d** (4.5 g, 11.5 mmol) in methanol with stirring at 0 °C. After the reaction mixture had been allowed to stand at room temperature, the crystals (**1f**) produced were filtered off. Recrystallization was carried out from methanol–ether. The results are summarized in Table 1.

*Z-D-Phg-L-Ser-NH$_2$ (**1i**)*: Amidation was carried out as follows. Dry ammonia gas was bubbled into a solution of **1h** (5 g, 12.9 mmol) in methanol at 0 °C until saturation. After the mixture had been allowed to stand at room temperature, the crystals (**1i**) produced were filtered off. Recrystallization was carried out from methanol–ether. The results are summarized in Table 1.

*Z-D-Phg-L-Thr-Gly-OBzl (**1g**)*: Dry hydrogen chloride gas was bubbled for 30 min at 0 °C into a solution of Boc-Thr-Gly-OBzl[1] (2.02 g, 6 mmol) in ethyl acetate (20 ml) containing anisole (1 ml). The reaction mixture was allowed to stand at room temperature for 30 min. After the reaction mixture had been concentrated under reduced pressure, anhydrous ether was added to the residual products. Crystals were obtained in theoretical yield. The hydrochloride, Z-D-Phg-OH(1.71 g, 6 mmol), Et_3N (0.83 ml, 6 mmol) was treated with DCC (1.24 g, 6 mmol) in THF at −10 °C for 4 h. After the reaction mixture had been allowed to stand overnight in a refrigerator, acetic acid (1 ml) was added. The *N*,*N*′-dicyclohexylurea produced was filtered off, and the filtrate was concentrated under reduced pressure. The residual oil was dissolved in ethyl acetate and the solution was washed successively with 1 M sodium hydrogencarbonate, 1 M hydrochloric acid, and water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The

oily products were crystallized from ethyl acetate–ether–hexane. **1g** was obtained 70.5% yield from Boc-Thr-Gly-OBzl.

Synthesis of O-Tosyl-N-acyl-β-hydroxy Amino Acid Peptide Derivatives (2). *Phenylacetyl-L-Thr(Tos)-Gly-OBzl(2c)*: *O*-tosylation was carried out as follows. A solution of tosyl chloride (3.73 g, 30 mmol) in dry pyridine (10 ml) was added drop by drop with stirring at −10 °C to a solution of **1c** (3.84 g, 10 mmol) in dry pyridine (30 ml). When the addition was over, the reaction mixture was allowed to stand at −10 °C for 3 days. It was then concentrated under reduced pressure, and the residual products were dissolved in ethyl acetate. The solution was washed with water and dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crystals (**2c**) produced were recrystallized from ethyl acetate–ether–hexane. The results are recrystallized from ethyl acetate–ether–hexane. The results are summarized in Table 2.

Detosylation of O-Tosyl Peptide Derivatives (2). *2-[α-(Benzyloxycarbonylamino)benzyl]-4-methylcarbamoyl-2-oxazoline (3-9)*: Detosylation was carried out as follows. A solution of **2j** (3.5 g, 6.5 mmol) and Et_3N (1.86 ml, 13 mmol) was refluxed at 70 °C for 3 days. After the solvent had been evaporated under reduced pressure, the oily product was dissolved in ethyl acetate. The solution was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residual product (**3**-9) was crystallized from ethyl acetate–ether. The results are summarized in Tables 3 and 4. NMR ($CDCl_3$): δ; 2.62 ppm (3H d, 4.9 Hz, -NHC$\underline{H}_3$); 4.35, 4.39, 4.53 ppm (3H 3q, 6.0, 12 Hz, 4.5, 12 Hz, 4.5, 6.0 Hz, -C$\underline{H}_2$-C$\underline{H}$-); 5.06 ppm (2H s, C_6H_5-C$\underline{H}_2$-); 5.43 ppm (1H d, 8.5 Hz, C_6H_5C$\underline{H}$=).

2-Benzyl-4-[(ethoxycarbonyl)methylcarbamoyl]-5-methyl-2-oxazoline (3-2): **2b** (8.19 g, 17.6 mmol) and Et_3N (4.9 ml, 35.2 mmol) were treated in THF as in the synthesis of **3**-9. The crude product was crystallized from ethyl acetate–ether. A small amount of crystals appeared were collected by filtration. The crystals were identified as Phenylacetyl-D-Thr-Gly-OEt [mp 147—148 °C, $[\alpha]_D^{23}$ −6.5° (*c* 1.0, DMF)]. **3**-2 was isolated from the mother liquor by the addition of hexane (Table 3). **3**-2 NMR ($CDCl_3$): δ; 1.11 ppm (3H d, 5.5 Hz, C$\underline{H}_3$-CH=); 1.15 ppm (3H t, 7.0 Hz, C$\underline{H}_3$-C$\underline{H}_2$-); 3.60 ppm (2H s, C_6H_5C$\underline{H}_2$-); 3.84 ppm (2H d, 6.2 Hz, -NH-C$\underline{H}_2$-CO-); 4.07 ppm (2H q, 7.0 Hz, CH_3-C$\underline{H}_2$-); 4.80 ppm (2H m, CH_3-C$\underline{H}$-C$\underline{H}$-); 7.28 ppm (5H s, $C_6\underline{H}_5$-CH_2-).

2c also gave a trace amounts of Phenylacetyl-D-Thr-Gly-OBzl [mp 165—166 °C, $[\alpha]_D^{23}$ −10.6° (*c* 1.0, DMF)].

N-[α-(Benzyloxycarbonylamino)crotonylglycine Ethyl Ester (4-11) and Ethyl 5-Ethylidenehydantoin-3-acetate (5-11): **2m** (2.1 g, 4.26 mmol) and Et_3N (1.78 ml, 12.8 mmol) was treated in THF by the above detosylation procedure. The crude product having two components was subjected to silica gel chromatography developed by the mixed solvent, $CHCl_3$–ethyl acetate (2:1 v/v). The product of R_f 0.85[5] was **4**-11 and R_f 0.65[5] was **5**-11: **4**-11 NMR (DMSO-d_6): δ; 1.17 ppm (3H t, 7.0 Hz, C$\underline{H}_3$-C$\underline{H}_2$-); 1.63 ppm (3H d, 7.0 Hz, C$\underline{H}_3$-CH=); 3.81 ppm (2H d, 6.0 Hz, -NH-C$\underline{H}_2$-); 4.08 ppm (2H q, 7.0 Hz, CH_3-C$\underline{H}_2$-); 5.04 ppm (2H s, C_6H_5C$\underline{H}_2$-); 6.30 ppm (1H q, 7.0 Hz, CH_3-C$\underline{H}$=); 7.35 ppm (5H s, $C_6\underline{H}_5CH_2$-); 8.18 ppm (1H t, 6.0 Hz, -N$\underline{H}$-CH_2-); 8.52 ppm (1H s, -N$\underline{H}$-$\overset{\overset{O}{\|}}{C}$-), **5**-11 NMR ($CDCl_3$): δ; 1.26 ppm (3H t, 7.0 Hz, C$\underline{H}_3$-CH_2-); 1.83 ppm (3H d, 7.8 Hz, C$\underline{H}_3$-CH=); 4.23 ppm (2H q, 7.0 Hz, CH_3-C$\underline{H}_2$-); 4.29 ppm (2H s, =N-C$\underline{H}_2$-); 5.99 ppm (1H q, 7.8 Hz, CH_3-C$\underline{H}$=); 9.01 ppm (1H s, -N$\underline{H}$-CO-).

N-[α-(t-Butoxycarbonylamino)crotonyl]glycine Ethyl Ester (4-12) and 5-11: **2n** (2.1 g, 4.26 mmol) and Et_3N (1.78 ml, 12.8 mmol) was subjected to the above detosylation procedure. The crude product having two components was subjected to silica gel chromatography with use of the mixed solvent, $CHCl_3$–ethyl acetate (2:1 v/v). The product of R_f 0.85[5] was **4**-12 and that of R_f 0.64[5] was **5**-11: **4**-12 NMR (DMSO-d_6): δ; 1.18 ppm (3H t, 7.0 Hz, C$\underline{H}_3$-CH_2-); 1.39 ppm (9H s, $(C\underline{H}_3)_3$-C); 1.62 ppm (3H d, 7.0 Hz, C$\underline{H}_3$-CH=); 3.82 ppm (2H d, 6.0 Hz, -NH-C$\underline{H}_2$-CO-); 4.08 ppm (2H q, 7.0 Hz, CH_3-C$\underline{H}_2$-); 6.20 ppm (1H q, 7.0 Hz, CH_3-C$\underline{H}$=). Formation of a small amounts of **5**-11 was detected by thin layer chromatography, no isolation being carried out.

N-(Benzyloxycarbonyldehydroalanyl)glycine Ethyl Ester (4-13) and Ethyl 5-Methylenehydantoin-3-acetate (5-13): **2o** (1.9 g, 4 mmol) and Et_3N (1.1 ml, 8 mmol) were subjected to the above detosylation procedure in THF. The crude product having two components was subjected to silica gel chromatography with use of the mixed solvent, $CHCl_3$–ethyl acetate (1:1 v/v). The product of R_f 0.78[6] was **4**-13 and R_f 0.60[6] was **5**-13: **4**-13 NMR ($CDCl_3$): δ; 1.24 ppm (3H t, 7.1 Hz, C$\underline{H}_3$-CH_2-); 4.02 ppm (2H d, 5.5 Hz, -NH-C$\underline{H}_2$-CO-); 4.19 ppm (2H q, 7.1 Hz, CH_3-C$\underline{H}_2$-); 5.12 ppm (2H s, C_6H_5C$\underline{H}_2$-); 5.21, 6.08 ppm (1H m, 1H d, 2.0 Hz, C$\underline{H}_2$=$\dot{C}$-); 7.33 ppm (5H s, $C_6\underline{H}_5CH_2$-), **5**-13 NMR ($CDCl_3$): δ; 1.25 ppm (3H t, 6.5 Hz, C$\underline{H}_3$-CH_2-); 4.22 ppm (2H q, 6.5 Hz, CH_3-C$\underline{H}_2$-); 4.28 ppm (1H s, =N-C$\underline{H}_2$-); 4.90 ppm (2H m, C$\underline{H}_2$=$\dot{C}$-); 8.42 ppm (1H s, -N$\underline{H}$-CO-).

N-(t-Butoxycarbonyldehydroalanyl)glycine Benzyl Ester (4-14): **2p** (1.45 g, 3 mmol) and Et_3N (0.83 ml, 6 mmol) were subjected to the above detosylation procedure in THF. The crude product was purified by means of silica gel chromatography with use of the mixed solvent, $CHCl_3$–ethyl acetate (1:1 v/v). **4**-14 NMR ($CDCl_3$): δ; 1.45 ppm (9H s, $(C\underline{H}_3)_3$-C); 4.12 ppm (2H d, 5.0 Hz, -NH-C$\underline{H}_2$-CO-); 5.10 ppm, 6.02 ppm (1H m, 1H d, 2 Hz, C$\underline{H}_2$=$\dot{C}$-); 5.19 ppm (2H s, C_6H_5C$\underline{H}_2$-); 7.34 ppm (5H s, $C_6\underline{H}_5CH_2$-).

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5) Thin layer chromatography solvent system. $CHCl_3$–AcOEt (2:1 v/v).

6) Thin layer chromatography solvent system. $CHCl_3$–AcOEt (1:1 v/v).