

Studies on 2-Aziridinecarboxylic Acid. VII.¹⁾ Formation of Dehydroamino Acid Peptides *via* Isomerization of Peptides Containing 2-Aziridinecarboxylic Acid by Tertiary Amines

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Peptides containing 1-(α -aminoacyl)-2-aziridinecarboxylic acid were isomerized into the corresponding dehydroamino acid peptides by treatment with the tertiary amines, triethylamine or 1,4-diazabicyclo[2.2.2]octane (Dabco). Dehydrohydantoin derivatives were also prepared by treatment of benzyloxycarbonyl-2-aziridinecarboxylic acid derivatives with tertiary amines.

Recently many biologically active peptides containing dehydroamino acid (DHA) have been isolated and much attention has been directed to their synthesis. Literature concerning the synthesis of DHA peptides has mainly dealt with β -elimination of the O-leaving group of β -hydroxy α -amino acid derivatives,²⁾ and a more recent paper has reported Hofmann degradation reaction of 2,3-diaminopropionic acid derivatives.³⁾

In the previous paper,⁴⁾ we reported the isomerization of peptides containing 2-aziridinecarboxylic acid (Azyline, Azy) and 3-methyl-2-aziridinecarboxylic acid (3-MeAzy) into the corresponding DHA peptides with NaI in an acetone solution. During our investigation on the reaction of Azy peptides with several amines, we

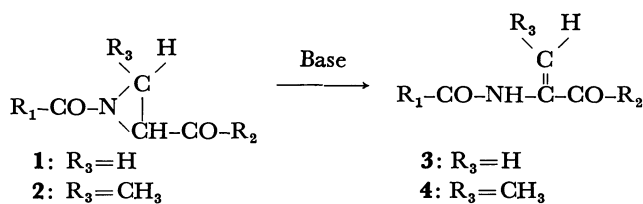
found that they react with primary and secondary amines to form the corresponding amine adducts, α,β -diaminopropionic acid derivatives,⁵⁾ and the *trans*-acylation reaction occurs due to peptide bond cleavage.⁵⁾ Also, 1-acyl- and 1-(α -aminoacyl)-2-aziridinecarboxylic acid peptides are isomerized into the corresponding DHA peptides upon treatment with tertiary amines as in the reaction with NaI.

In the present study the reactions of Azy peptides with the tertiary amines, triethylamine and Dabco were observed in detail. The Azy and 3-MeAzy peptides used as the starting materials were synthesized by the mixed anhydride method from N-protected amino acid and Azy derivatives according to the procedure described

TABLE 1. YIELDS AND PROPERTIES OF Azy-PEPTIDES (1, 2, 5)

Azy peptide ^{a)} ↓	Yield/%	Mp $\theta_m/^\circ\text{C}$	$[\alpha]_D^{25}/^\circ$	Found (Calcd) (%)		
				C	H	N
Z-Gly-Azy-NHCH ₃ (1a)	70	193 (decomp)	−38.0 (c 0.8, MeOH)	57.84 (57.72)	5.81 5.88	14.38 14.43
Z-Gly-Azy-NHBzl (1b)	72	122.5–123.5	−90.0 (c 1.1, CHCl ₃)	66.42 (66.48)	5.53 5.58	11.11 11.08
Z-Phe-Azy-NHCH ₃ (1c)	56	170–171	−66.9 (c 1.1, CHCl ₃)	66.08 (66.13)	6.12 6.08	11.13 11.02
Z-Ala-Azy-OBzl (1d)	83	58–61	−50.9 (c 1.0, DMSO)	65.91 (65.96)	5.73 5.80	7.29 7.33
Z-Phe-Azy-OBzl (1e)	72	68–69	−62.7 (c 1.0, DMSO)	70.69 (70.73)	5.68 5.72	6.16 6.11
Z-Gly-Azy-Gly-OBzl (1f)	92	118–119	−52.5 (c 1.0, MeOH)	62.23 (62.16)	5.40 5.45	9.92 9.88
Z-Phe-3-MeAzy-NHCH ₃ (2a)	77	129–130	−25.3 (c 1.1, CHCl ₃)	66.81 (66.82)	6.27 6.37	10.69 10.63
Z-Phe-3-MeAzy-NHBzl (2b)	62	157–157.5	−35.1 (c 0.23, CHCl ₃)	71.28 (71.32)	6.11 6.20	8.83 8.91
Z-Phe-3-MeAzy-OBzl (2c)	80	95–97	−61.1 (c 1.0, MeOH)	71.26 (71.17)	6.02 5.97	5.89 5.93
Z-Gly-3-MeAzy-Gly-OBzl (2d)	90	123.5–124.5	−58.2 (c 1.0, AcOEt)	62.88 (62.86)	5.70 5.73	9.68 9.56
Z-Ala-3-MeAzy-Gly-OBzl (2e)	93	110–111	−59.7 (c 1.0, CHCl ₃)	63.48 (63.50)	5.98 6.00	9.30 9.27
Z-Azy-Gly-OBzl (5a)	60	109–110	−50.6 (c 1.0, MeOH)	65.17 (65.21)	5.50 5.47	7.71 7.60
Boc-Azy-Gly-OBzl (5b)	61	71–71.5	−80.4 (c 1.0, MeOH)	61.22 (61.07)	6.85 6.63	8.35 8.34
Z-3-MeAzy-Gly-OBzl (5c)	73	62–64	−63.2 (c 1.0, MeOH)	65.95 (65.96)	5.83 5.80	7.42 7.33
Boc-3-MeAzy-Gly-OBzl (5d)	79	89.5–90	−70.0 (c 1.0, MeOH)	66.21 (66.06)	7.24 7.34	8.01 8.04

a) All Azy peptides were synthesized by the mixed anhydride method except **5a–d**. Arrow indicates final coupling position. Azy: (2*S*)-form, 3-MeAzy: (2*S*, 3*S*)-form.

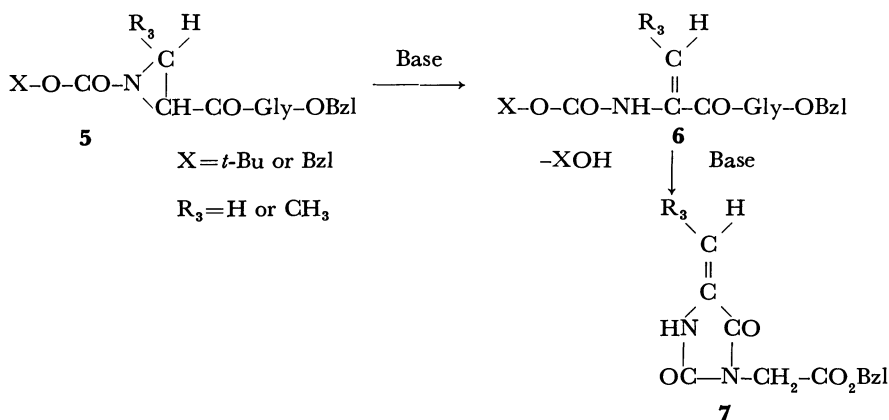


Scheme 1.

TABLE 2. YIELDS AND PROPERTIES OF DHA-PEPTIDES (**3**, **4**)

Product (3 , 4)	Yield/%	Mp $\theta_m/^\circ\text{C}$	Base ^{a)}	Found (Calcd) (%)				NMR data of DHA		
				C	H	N	NH	δ , DMSO- d_6 =CH ₂	CH ₃	
Z-Gly- Δ Ala-NHCH ₃ (3a)	89	175 (decomp)	Et ₃ N(3)	57.84 57.72	5.81 5.88	14.38 14.43	9.01	5.58	6.20	—
Z-Gly- Δ Ala-NHBzl (3b)	84	117.5—118.5	Et ₃ N(3)	66.42 66.48	5.53 5.58	11.11 11.08	9.07	5.60	6.24	—
Z-Phe- Δ Ala-NHCH ₃ (3c)	100	syrup	Et ₃ N(6)	66.08 66.13	6.12 6.08	11.13 11.02	8.58	6.30	6.60	— ^{b)}
Z-Ala- Δ Ala-OBzl (3d)	100	syrup	Et ₃ N(3)	65.91 65.96	5.73 5.80	7.29 7.33	8.34	5.92	6.56	— ^{b)}
Z-Phe- Δ Ala-OBzl (3e)	100	syrup	Et ₃ N(3)	70.69 70.73	5.68 5.72	6.16 6.11	8.12	5.92	6.60	— ^{b)}
Z-Gly- Δ Ala-Gly-OBzl (3f)	100	133—136	Et ₃ N(6)	62.23 62.16	5.40 5.45	9.92 9.88	8.99	5.57	6.31	—
Z-Phe- Δ Aba-NHCH ₃ (4a)	77	165—167	Dabco(24)	66.81 66.82	6.27 6.37	10.69 10.63	9.05	—	6.36q	1.40d
Z-Phe- Δ Aba-NHBzl (4b)	88	162.5—163.5	Dabco(24)	71.28 71.32	6.11 6.20	8.83 8.91	9.15	—	6.44q	1.40d
Z-Phe- Δ Aba-OBzl (4c)	90	151—152	Dabco(6)	71.26 71.17	6.02 5.97	5.89 5.93	9.20	—	6.67q	1.68d
Z-Gly- Δ Aba-Gly-OBzl (4d)	87	101—102	Dabco(24)	62.88 62.86	5.70 5.73	9.68 9.56	9.01	—	6.55q	1.66d
Z-Ala- Δ Aba-Gly-OBzl (4e)	87	139—140.5	Dabco(24)	63.48 63.50	5.98 6.00	9.30 9.27	9.02	—	6.52q	1.65d

a) The reaction was carried out in a CHCl₃ solution at 35 °C and the base used was 2 equivmolar against Azy peptide. The values in parenthesis are the reaction time/h. b) NMR spectrum in CDCl₃.



Scheme 2.

in our previous papers.⁵⁻⁷⁾ Their properties and yields are summarized in Table 1 and the reaction procedure of the Azy peptides with amines is shown in Scheme 1.

Azy and 3-MeAzy peptides (**1a—f** and **2a—e**) were treated with 2 equivmolar amount of tertiary amine (Et₃N or Dabco) in CHCl₃ solution at 35 °C for 3—24 h, and then the corresponding dehydroamino acid (DHA, Δ Ala) derivatives were isolated by silica-gel column

chromatography. The DHA produced was identified by NMR.

In the NMR data, characteristic signals of the DHA structure appeared at δ 5.5—5.9 for the vinyl proton of dehydroalanine (Δ Ala), and at δ 1.4—1.7 as a doublet for the methyl proton and at δ 6.3—6.8 as a quartet for the β -proton of dehydro- α -aminobutyric acid (Δ Aba). Δ Aba was of the (Z)-configuration. The product (**3**, **4**)

TABLE 3. Boc- AND Z- Δ Ala-Gly-OBzl (6) AND DEHYDROHYDANTOIN (7)

Azy peptide (5)	Base	React time/h	Product yields/%	
			DHA (6)	Hydantoin (7)
Z-Azy-Gly-OBzl (5a)	Et ₃ N	12	—	75
	Dabco	6	—	80
Boc-Azy-Gly-OBzl (5b)	Et ₃ N	24	95	—
	Dabco	6	100	—
Z-3-MeAzy-Gly-OBzl (5c)	Et ₃ N	7 ^{a)}	—	—
	Dabco	3 ^{a)}	68	28
Boc-3-MeAzy-Gly-OBzl (5d)	Et ₃ N	7 ^{a)}	—	—
	Dabco	4 ^{a)}	85	—

a) Reaction time/d.

of the isomerization of the Azy peptides are summarized in Table 2.

The reaction results show that 1-acyl-2-aziridine-carboxylic acid peptides (1a–f) were easily isomerized into the corresponding Δ Ala peptides (3a–f) by the treatment of triethylamine, but contrary to our expectation, 1-acyl-3-methyl-2-aziridinecarboxylic acid peptides (2a–e) were not isomerized into the Δ Aba peptides (4a–e), even after 7 d of treatment. Use of the more basic Dabco as an isomerizing reagent was necessary to obtain Δ Aba peptides (4a–e).

This isomerization reaction seems to be induced by a direct withdrawing of the α -proton of Azy or 3-MeAzy with base. The α -proton of unsubstituted Azy (1a–f) could be easily withdrawn by Et₃N treatment, but not that of the substituted 3-MeAzy (2a–e) because of the methyl group on the aziridine ring. Thus, the more basic Dabco was needed to withdraw the α -proton of 3-MeAzy for its isomerization.

We also examined the reaction of 1-benzoyloxycarbonyl- and 1-*t*-butoxycarbonyl-2-aziridinecarboxylic acid peptides (5a–d) with amines. As shown in Scheme 2 and Table 3, the reaction of the Azy peptides blocked by urethane-type groups with tertiary amines afforded not only the corresponding DHA peptides, but also dehydrohydantoin derivatives (7a, 7b). Again, the 3-MeAzy peptides (5c, 5d) were not isomerized with Et₃N and the benzoyloxycarbonyl derivatives were more easily isomerized into the corresponding DHA peptides than the *t*-butoxycarbonyl peptides. The results of the dehydrohydantoin (7) formation reaction, which occurred *via* reaction of the DHA peptides produced by the reaction with tertiary amines, agreed very well with the results of the β -elimination reaction of O-activated Z-Ser- or Z-Thr- derivatives found by Campbell and Behr,⁸⁾ us,⁹⁾ and, Shin *et al.*¹⁰⁾ Thus the benzoyloxycarbonyl group of the aziridine is more labile than the *t*-butoxycarbonyl group in the basic conditions, that is, Z-Azy-Gly-OBzl (5a) and Z-3-MeAzy-Gly-OBzl (5c) isomerized more easily than Boc-Azy-Gly-OBzl (5b) and Boc-3-MeAzy-Gly-OBzl (5d) as shown in Table 3. The benzoyloxycarbonyl group attached to the unsubstituted aziridinecarboxylic acid (5a) seemed to be very labile and Z- Δ Ala-Gly-OBzl could not be isolated after the reaction of 5a with tertiary amine, even in Et₃N.

From the isomerization reaction of Azy and 3-MeAzy described above, it is concluded that Azy and 3-MeAzy

has a distinctly different reactivity against tertiary amines and the isomerization by the tertiary amines, which can be used to the selective synthesis of DHA peptides, differs from that by NaI or the synthesis of DHA peptides *via* β -elimination of β -hydroxy α -amino acid.

Experimental

Uncorrected melting points are reported. The homogeneity of the products was checked by thin-layer chromatography on silica-gel plates. The optical rotations were determined at the D line on a Perkin-Elmer 141 polarimeter. The NMR spectra were obtained with a Hitachi R20B high-resolution NMR spectrometer, the chemical shifts being obtained using TMS as the internal reference. All the *N*-aminoacyl Azy and 3-MeAzy peptides used in this study were synthesized by the method described in literature,^{6,7)} and their properties and yield are summarized in Table 1.

(2*S*)-Z-Azy-Gly-OBzl (5a). To a solution of (2*S*)-H-Azy-Gly-OBzl¹¹⁾ (1.63 g, 6.96 mmol) and Et₃N (0.97 ml, 6.96 mmol) in CHCl₃ (15 ml), was added Z-ON¹¹⁾ (1.95 g, 6.96 mmol) with stirring at 0 °C. After being stirred overnight at 25 °C, the solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with 10% citric acid, 1 M NaHCO₃ and water, and dried over Na₂SO₄, concentrated *in vacuo*. The residue was crystallized from ethyl acetate-hexane, 1.53 g (60%) of 5a was obtained, mp 109–110 °C, [α]_D²³ –50.6° (*c* 1.0, MeOH). NMR (CDCl₃) δ : 2.38 (1H q, J_{gem} =0.8 Hz, J_{trans} =3.5 Hz, Azy β -proton), 2.53 (1H q, J_{gem} =0.8 Hz, J_{cis} =6.3 Hz, Azy β -proton), 3.07 (1H q, J_{trans} =3.5 Hz, J_{cis} =6.3 Hz, Azy α -proton). Z-ON can be replaced with Z-Cl.¹¹⁾

Found: C, 65.17; H, 5.50; N, 7.71%. Calcd for C₂₀H₂₀O₅N₂: C, 65.21; H, 5.47; N, 7.60%.

(2*S*)-Boc-Azy-Gly-OBzl (5b). To a solution of (2*S*)-H-Azy-Gly-OBzl¹¹⁾ (4.0 g, 17.1 mmol) and Et₃N (2.38 ml, 17.1 mmol) in CHCl₃ (50 ml), was added Boc-ON¹¹⁾ (4.63 g, 18.8 mmol) with stirring at 0 °C. After the reaction mixture had been worked up as described above, the product was crystallized from ethyl acetate-hexane, 3.51 g (61.3%) of 5b was obtained, mp 71.0–72.5 °C, [α]_D²³ –80.4° (*c* 1.0, MeOH). NMR (CDCl₃) δ : 2.30 (1H q, J_{gem} =0.8 Hz, J_{trans} =3.8 Hz, Azy β -proton), 2.49 (1H q, J_{gem} =0.8 Hz, J_{cis} =6.6 Hz, Azy β -proton), 3.03 (1H q, J_{trans} =3.8 Hz, J_{cis} =6.6 Hz, Azy α -proton).

Found: C, 61.22; H, 6.85; N, 8.35%. Calcd for C₁₇H₂₂O₅N₂: C, 61.07; H, 6.63; N, 8.34%.

(2*S*, 3*S*)-Z-3-MeAzy-Gly-OBzl (5c). To a solution of (2*S*, 3*S*)-H-3-MeAzy-Gly-OBzl¹¹⁾ (1.87 g, 7.54 mmol) and Et₃N (1.05 ml, 7.54 mmol) in CHCl₃ (15 ml), was added

Z-ON¹¹ (1.95 g, 7.54 mmol) with stirring at 0 °C. The reaction mixture was stirred overnight and worked up as described above. The product was crystallized from ethyl acetate-hexane, 2.10 g (72.8%) of **5c** was obtained, mp 62–64 °C, $[\alpha]_D^{25} -63.2^\circ$ (c 1.0, MeOH). NMR (CDCl₃) δ : 1.28 (3H d, $J=5.5$ Hz, CH₃), 2.79 (1H m, 3-MeAzy, β -proton), 3.14 (1H d, $J=7.0$ Hz, 3-MeAzy, α -proton). Z-ON can be replaced with Z-Cl.

Found: C, 65.96; H, 5.83; N, 7.42%. Calcd for C₂₁H₂₂O₅N₂: C, 65.96; H, 5.80; N, 7.33%.

(2S, 3S)-Boc-3-MeAzy-Gly-OBzl (**5d**). To a solution of (2S, 3S)-H-3-MeAzy-Gly-OBzl¹⁷ (1.25 g, 5.06 mmol) and Et₃N (0.70 ml, 5.06 mmol) in CHCl₃ (15 ml), was added Boc-ON¹¹ (1.40 g, 6.07 mmol) with stirring at 0 °C. The reaction mixture was stirred overnight and worked up as described above. The product was crystallized from ethyl acetate-hexane, 1.38 g (78.5%) of **5d** was obtained, mp 89.5–90.0 °C, $[\alpha]_D^{25} -70.0^\circ$ (c 1.0, MeOH). NMR (CDCl₃) δ : 1.27 (3H d, $J=5.5$ Hz, CH₃), 2.74 (1H m, 3-MeAzy β -proton), 3.09 (1H d, $J=6.4$ Hz, 3-MeAzy α -proton).

Found: C, 62.21; H, 6.88; N, 8.01%. Calcd for C₁₈H₂₄O₅N₂: C, 62.06; H, 6.94; N, 8.04%.

Z-Gly- Δ Ala-NHBzl (**3b**). *General Isomerization Procedure of Azy with Et₃N*: A solution of **1b** (100 mg, 0.27 mmol) and Et₃N (0.08 ml, 0.54 mmol) in CHCl₃ (5 ml) was stirred at 35 °C for 3 h. After the solvent had been removed *in vacuo*, the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with 10% citric acid and water, and then dried over Na₂SO₄, concentrated *in vacuo*. After the obtained residue was purified by the silica-gel column chromatography, the product was crystallized from CHCl₃-ether-hexane, 84.3 mg (84.3%) of **3b** was obtained, mp 117.5–118.5 °C.

Z-Gly- Δ Aba-Gly-OBzl (**4d**). *General Isomerization Procedure of 3-MeAzy with Dabco*: A solution of **2d** (200 mg, 0.45 mmol) and Dabco (102 mg, 0.91 mmol) in CHCl₃ (5 ml) was stirred at 35 °C for 24 h. After the reaction mixture had been worked up as described above, the residue was crystallized from ethyl acetate-hexane, 174 mg (87%) of **4d** was obtained, mp 101–102 °C [lit, mp 102–104 °C⁴¹].

Benzyl 5-Methylenedihydantoin-3-acetate (**7a**). *Using Et₃N*: A solution of **5a** (200 mg, 0.54 mmol) and Et₃N (0.15 ml, 1.09 mmol) in CHCl₃ (3 ml) was stirred at 35 °C for 12 h. After the reaction mixture had been worked up as described above, the residue was purified with silica-gel column chromatography and was crystallized from ethyl acetate-ether-hexane, 105 mg (75%) of **7a** was obtained, mp 171–172 °C. NMR (CDCl₃) δ : 4.32 (2H s), 4.92, (1H d, $J=1.8$ Hz), 5.15, 5.17 (4H 2s), 5.42 (1H d, $J=1.8$ Hz), 7.32 (5H s), 8.35 (1H bs).

Found: C, 60.05; H, 4.72; N, 10.72%. Calcd for C₁₃H₁₂O₄N₂: C, 59.99; H, 4.65; N, 10.77%.

Z- Δ Ala-Gly-OBzl (**6a**) could not be prepared by this procedure.

Using Dabco: A solution of **5a** (200 mg, 0.54 mmol) and Dabco (121 mg, 1.08 mmol) in CHCl₃ (3 ml) was stirred at 35 °C for 6 h. After the reaction mixture had been worked up as described above, 112 mg (80%) of **7a** was obtained. **6a** could not be prepared.

Boc- Δ Ala-Gly-OBzl (**6b**). *Using Et₃N*: A solution of **5b** (100 mg, 0.29 mmol) and Et₃N (0.08 ml, 0.58 mmol) in CHCl₃ (3 ml) was stirred at 35 °C for 24 h. After the reaction mixture had been worked up as described above, 95 mg (95%) of **6b** was obtained as an oily material. NMR (CDCl₃) δ : 1.48 (9H s), 4.12 (2H d, $J=5.0$ Hz), 5.15 (1H m), 5.18 (2H s), 6.00 (1H d, $J=1.8$ Hz), 6.78 (1H bt), 7.25 (1H bs), 7.32 (5H s).

Found: C, 61.15; H, 6.72; N, 8.28%. Calcd for C₁₇H₂₂O₅N₂: C, 61.07; H, 6.63; N, 8.34%. **7b** could not be prepared.

Using Dabco: A solution of **5b** (300 mg, 0.86 mmol) and

Dabco (194 mg, 1.73 mmol) in CHCl₃ (5 ml) was stirred at 35 °C for 6 h. After the reaction mixture had been worked up as described above, 300 mg (100%) of **6b** was obtained as an oily material. **7b** could not be prepared.

Z- Δ Aba-Gly-OBzl (**6c**) and Benzyl 5-Ethylidenedihydantoin-3-acetate (**7c**). *Using Dabco*: A solution of **5c** (200 mg, 0.5 mmol) and Dabco (112 mg, 1 mmol) in CHCl₃ (3 ml) was stirred at 35 °C for 3 d. After the reaction mixture had been worked up as described above, the crude product of two components was subjected to silica-gel column chromatography developed by CHCl₃, yielding 136 mg (68%) of **6c**, mp 99–100 °C, and 38 mg (28%) of **7c**, mp 186–186.5 °C. **6c**:

NMR (CDCl₃) δ : 1.70 (3H d, $J=7.0$ Hz), 4.16 (2H d, $J=5.5$ Hz), 5.12 (2H s), 5.20 (2H s), 6.52 (1H q, $J=7.0$ Hz), 6.76 (1H bs), 7.30 (10H s), 7.00 (1H bs), 7.15 (1H bs). **7c**: NMR (CDCl₃) δ : 1.83 (3H d, $J=7.5$ Hz), 4.35 (2H s), 5.19 (2H s), 5.98 (1H q, $J=7.5$ Hz), 7.32 (5H s), 9.05 (1H bs).

6c; Found: C, 66.02; H, 5.86; N, 7.23%. Calcd for C₂₁H₂₂O₅N₂: C, 65.96; H, 5.80; N, 7.33%.

7c; Found: C, 61.28; H, 5.20; N, 10.32%. Calcd for C₁₄H₁₄O₄N₂: C, 61.31; H, 5.15; N, 10.21%.

Using Et₃N: A solution of **5c** (200 mg, 0.5 mmol) and Et₃N (0.14 ml, 1 mmol) in CHCl₃ (3 ml) was stirred at 35 °C for 7 d. No reaction occurred and only **5c** was recovered.

Boc- Δ Aba-Gly-OBzl (**6d**). *Using Dabco*: A solution of **5d** (200 mg, 0.57 mmol) and Dabco (128 mg, 1.14 mmol) in CHCl₃ (3 ml) was stirred at 35 °C for 4 d. After the reaction mixture had been worked up as described above, 170 mg (85%) of **6d** was obtained, mp 119.5–120.5 °C. NMR (CDCl₃) δ : 1.45 (9H s), 1.75 (3H d, $J=7.0$ Hz), 4.14 (2H d, $J=5.5$ Hz), 5.20 (2H s), 6.49 (1H q, $J=7.0$ Hz), 6.69 (1H bs), 7.34 (5H s), 7.28 (1H bs).

Found: C, 62.18; H, 6.81; N, 8.12%. Calcd for C₁₈H₂₄O₅N₂: C, 62.06; H, 6.94; N, 8.04%.

7d could not be prepared.

Using Et₃N: A solution of **5d** (100 mg, 0.29 mmol) and Et₃N (0.08 ml, 0.58 mmol) in CHCl₃ (3 ml) was stirred at 35 °C for 7 d. No reaction occurred and only **5d** was recovered.

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