Synthesis of Tripeptides Containing α,α-Diphenylglycine by the Modified Ugi Reaction

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Abstract: The modified Ugi reaction has been developed to synthesize tripeptides containing α,α-diphenylglycine (Dph) together with bulky amino acids. By the use of diphenylmethanimine, *N*-benzyloxycarbonyl (Z) amino acids and isocyanides derived from amino acids, very crowded tripeptides such as Z-Aib-Dph-Aib-OMe, Z-Ac_6c-Dph-Aib-OMe, Z-Dph-Dph-Dph-OMe, etc. have been synthesized.

Key words: α,α-diphenylglycine (Dph), α,α-disubstituted glycines, diphenylmethanimine, Ugi reaction, tripeptides

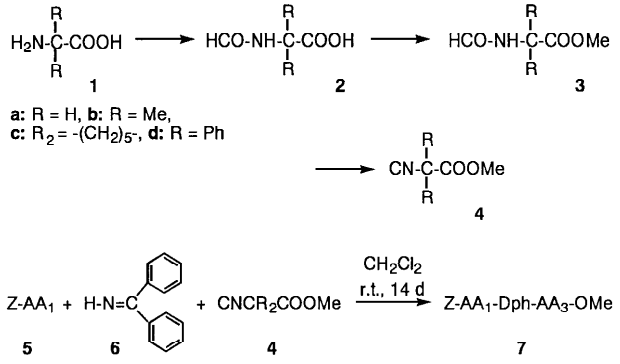
Peptides containing α,α-disubstituted glycines (DSGs) are of increasing interest in structure-activity studies of drugs based on hormone analogs or enzyme inhibitors, since DSGs restrict the conformational mobility of the peptide backbone and enhance resistance to the enzymatic degradation of peptides.[1] The synthesis of peptides containing DSGs, however, still provides challenging problems because of difficulties arising from steric hindrance in the conventional synthesis of their peptides.[1, 2] In order to overcome these difficulties, we recently applied high pressure conditions (9 kbar) to the Ugi reaction,[3] particularly to the modified Ugi reaction in which Schiff's bases prepared from amine and ketone components were used, and, thereby, we succeeded in synthesizing tripeptides containing the α,α-diisopropylglycine (Dip) residue.[4]

α,α-Diphenylglycine (Dph), one of the DSGs, is of interest as a very crowded, aromatic amino acid; α,α-dibenzylglycine (Dbz) is also of interest.[5, 7] Although Dph is commercially available, the only Dph-containing peptide so far reported is a Dph-Gly segment.[6, 7] Recently we successfully synthesized a number of dipeptides in which Dph was coupled with various amino acids (AA), by screening a variety of coupling methods.[8] However, tripeptides, in the middle of which Dph is contained, such as **7**, were found to be hardly obtained by these coupling methods, particularly in the cases when the AAs are bulky. On the other hand, removal of an *N*-benzyl group by catalytic hydrogenolysis from the tripeptide containing an *N*-benzyl-Dph residue obtained in the previous study[4] gave a sluggish reaction and complicated by-products.

In the present paper, we report the synthesis of various tripeptides containing Dph by employing the modified Ugi reaction in which diphenylmethanimine[9] **(6)** was well used as a Schiff's base without an *N*-benzyl group.

The modified Ugi reactions for synthesis of Dph-peptides were firstly carried out by using an *N*-(benzyloxycarbonyl)amino acid **5**, diphenylmethanimine **(6)**, and methyl isocyanoacetate[10] **(4a)** in dichloromethane or methanol at room temperature for 7–14 days. A variety of tripeptides **7** which contain various amino acids (AA_1) at the *N*-terminal of Dph could be obtained (Table 1). It is noteworthy that some peptides in which Dph combines with bulky amino acids, such as Val, α-aminoisobutyric acid (Aib), 1-aminocyclopentanecarboxylic acid (Ac_5c), 1-aminocyclohexanecarboxylic acid (Ac_6c), and Dph, were obtained in moderate or lower yields.

Previously we revealed that using high pressure conditions can effectively accelerate sluggish peptide-bond formation on sterically crowded substrates.[11] Hence, in this study the above reactions were also performed at high pressure, 0.9 GPa (9 kbar), using a stainless steel high pressure apparatus[4]. However, the yields at high pressure did not exceed those at atmospheric pressure (Table 1). In these cases, high pressure conditions seem to scarcely affect the yield.



Next, we prepared other isocyanides (**4b**, **4c** and **4d**) from *N*-formyl-Aib methyl ester **(2b)**, *N*-formyl-Ac_6c methyl ester **(2c)**, and *N*-formyl-Dph methyl ester **(2d)**, in order to synthesize DSG-containing peptides having much more crowded side chains. The isocyanide **4b** reacted fairly well with the *N*-Z derivative **5** of DSG, such as Aib, Ac_5c and Dph, and **6**, affording some tripeptides **7i–m** (AA_3 = Aib), in which crowded DSGs are linked successively (Table 2). When using the isocyanide **4c** derived from Ac_6c, the desired tripeptides **7n–r** could also be obtained, though mostly in yields lower than those of the corresponding Aib-containing peptides (Table 2). Interestingly, the yield of **7p** was rather better under high pressure conditions than under atmospheric conditions.

The isocyanide **4d** was prepared from Dph through 3 steps in the good, overall yield of 48%. Further, another Dph-equivalent isocyanide derivative **11** was also obtained through the product **10** in the modified Ugi reaction using **6**. The modified Ugi reactions using **4d** or **11** were carried out under high pressure, affording the desired tripeptides **7s–u and 14** (AA_3 = Dph). This is the first synthesis of homooligomers of Dph (**7v** and **14**). The tripeptide **14** was

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Table 1. Synthesis of Z-AA_1-Dph-Gly-OMe **7a–h**

Product	AA_1	AA_3	Yield (%)[a] (Solvent)[b]	mp (°C) (Solvent)[c]	$[\alpha]_D^{25}$ (c = 1, MeOH)	Molecular Formula[d]	^{1}H NMR ($CDCl_3$) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ
7a	Ala	Gly	51 44[e2]	144–145 (EtOAc)	–30.4	$C_{28}H_{29}N_3O_6$ (503.6)	1.35 (d, 3H, J = 7.2, Ala-βCH_3), 3.70 (s, 3H, OCH_3), 4.01 (d, 2H, J = 5.4, Gly-CH_2), 4.29 (br, 1H, Ala-αCH), 5.09 (d, 1H, J = 12.3, Z-CH_2), 5.10 (d, 1H, J = 12.3, Z-CH_2), 5.30 (br, 1H, Ala-NH), 6.44 (br, 1H, Gly-NH), 7.3–7.4 (m, 15H, arom), 7.82 (s, 1H, Dph-NH)	18.5 (Ala-βC), 41.9 (Gly-αC), 51.1 (Ala-αC), 52.4 (OCH_3), 66.9 (Z-CH_2), 70.5 (Dph-αC), 128.0, 128.07, 128.13, 128.2, 128.3, 128.4, 128.5, 136.2, 139.1, 139.3 (arom), 155.9 (Z-C=O), 169.6, 170.6, 171.7 (C=O)
7b	Val	Gly	53 36[e1] (EtOAc/hexane)[1]	foamy solid	–30.0	$C_{30}H_{33}N_3O_6$ (531.6)	0.76 (d, 3H, J = 6.9, Val-γCH_3), 0.84 (d, 3H, J = 6.9, Val-γCH_3), 2.07 (o, 1H, J = 6.9, Val-βCH), 3.70 (s, 3H, OCH_3), 3.99 (dd, 1H, J = 18.3, 5.4, Gly-CH_2), 4.01 (dd, 1H, J = 18.3, 5.4, Gly-CH_2), 4.08 (br, 1H, Val-αCH), 5.12 (s, 2H, Z-CH_2), 5.26 (br, 1H, Val-NH), 6.39 (br, 1H, Gly-NH), 7.3–7.42 (m, 15H, arom), 7.81 (s, 1H, Dph-NH)	17.4, 19.1 (Val-γC), 31.1 (Val-βC), 41.9 (Gly-αC), 52.4 (OCH_3), 60.5 (Val-αC), 67.0 (Z-CH_2), 70.5 (Dph-αC), 128.0, 128.08, 128.12, 128.17, 128.21, 128.3, 128.5, 128.7, 136.3, 138.9, 139.1 (arom), 156.5 (Z-C=O), 169.5 (C=O × 2), 171.8 (C=O)
7c	Leu	Gly	44 43[e2] (EtOAc/hexane)[1]	oil	–21.8	$C_{31}H_{35}N_3O_6$ (545.6)	0.88 (d, 6H, J = 6.0, Leu-δCH_3 × 2), 1.44 (m, 1H, Leu-γCH), 1.57 (m, 2H, Leu-βCH_2), 3.70 (s, 3H, OCH_3), 4.01 (d, 2H, J = 5.4, Gly-CH_2), 4.24 (br, 1H, Leu-αCH), 5.09 (d, 1H, J = 12.6, Z-CH_2), 5.10 (br, 1H, Leu-NH), 5.13 (d, 1H, J = 12.6, Z-CH_2), 6.47 (br, 1H, Gly-NH), 7.3–7.4 (m, 15H, arom), 7.84 (s, 1H, Leu-NH)	21.9, 22.9 (Leu-δC), 24.6 (Leu-γC), 41.2 (Leu-βC), 41.9 (Gly-αC), 52.3 (OCH_3), 54.1 (Leu-αC), 67.0 (Z-CH_2), 70.5 (Dph-αC), 128.0, 128.09, 128.14, 128.20, 128.35, 128.41, 128.44, 128.5, 136.2, 139.1, 139.2 (arom), 156.2 (Z-C=O), 169.6, 170.6, 171.7 (C=O)
7d	Phe	Gly	55 43[e3] (EtOAc/hexane)[1]	oil	–12.5	$C_{34}H_{33}N_3O_6$ (579.7)	2.97 (dd, 1H, J = 13.8, 7.3, Phe-βCH_2), 3.04 (dd, 1H, J = 13.8, 7.3, Phe-βCH_2), 3.69 (s, 3H, OCH_3), 3.97 (d, 2H, J = 5.4, Gly-CH_2), 4.50 (br, 1H, Phe-αCH), 5.08 (d, 1H, J = 13.2, Z-CH_2), 5.10 (d, 1H, J = 13.2, Z-CH_2), 5.25 (br, 1H, Phe-NH), 6.39 (br, 1H, Gly-NH), 7.00 (br, 2H, Phe-*ortho*H × 2), 7.17 (m, 3H, Phe-*meta*H × 2, *para*H), 7.31 (s, 15H, arom), 7.70 (s, 1H, Dph-NH)	37.9 (Phe-βC), 41.8 (Gly-αC), 52.3 (OCH_3), 56.5 (Phe-αC), 67.0 (Z-CH_2), 70.5 (Dph-αC), 126.9, 128.0, 128.1, 128.3, 128.4, 128.48, 128.51, 128.7, 129.4, 136.0, 138.9, 139.1 (arom), 156.0 (Z-C=O), 169.0, 169.5, 171.5 (C=O)
7e	Aib	Gly	46 46[e2]	176–177 (EtOAc)		$C_{29}H_{31}N_3O_6$ (517.6)	1.47 (s, 6H, Aib-βCH_3 × 2), 3.68 (s, 3H, OCH_3), 4.01 (d, 2H, J = 5.4, Gly-CH_2), 5.09 (s, 2H, Z-CH_2), 5.43 (s, 1H, Aib-NH), 6.82 (br, 1H, Gly-NH), 7.3–7.4 (m, 15H, arom), 7.87 (s, 1H, Dph-NH)	25.1 (Aib-βC × 2), 41.8 (Gly-αC), 52.2 (OCH_3), 57.3 (Aib-αC), 66.8 (Z-CH_2), 70.1 (Dph-αC), 127.9, 128.1, 128.15, 128.2, 128.3, 128.5, 136.2, 139.9 (arom), 155.2 (Z-C=O), 169.7, 171.6, 172.3 (C=O)
7f	Ac_3c	Gly	10 (EtOAc/hexane)[2]	foamy solid		$C_{29}H_{29}N_3O_6$ (515.6)	0.97 (dd, 2H, J = 7.5, 4.8, Ac_3c-βCH × 2), 1.48 (dd, 2H, J = 7.5, 4.8, Ac_3c-βCH × 2), 3.69 (s, 3H, OCH_3), 3.99 (d, 2H, J = 5.4, Gly-CH_2), 5.15 (s, 2H, Z-CH_2), 5.61 (br, 1H, Ac_3c-NH), 6.69 (br, 1H, Gly-NH), 7.25–7.4 (m, 15H, arom), 8.31 (s, 1H, Dph-NH)	17.4 (Ac_3c-βC × 2), 36.4 (Ac_3c-αC), 41.9 (Gly-αC), 52.3 (OCH_3), 67.3 (Z-CH_2), 70.5 (Dph-αC), 128.0, 128.2, 128.3, 128.4, 128.6, 136.0, 139.7 (arom), 156.4 (Z-C=O), 169.7, 170.3, 172.0 (C=O)

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Table 1. (continued)

Product	AA_1	AA_3	Yield (%)[a] (Solvent)[b]	mp (°C) (Solvent)[c]	$[\alpha]_D^{25}$ (c = 1, MeOH)	Molecular Formula[d]	^{1}H NMR ($CDCl_3$) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ
7g	Ac_5c	Gly	13 10[e1]	164–166 (EtOAc)		$C_{31}H_{33}N_3O_6$ (543.6)	1.70 (br, 4H, Ac_5c-$\gamma CH_2 \times 2$), 1.83 (br, 2H, Ac_5c-$\beta CH \times 2$), 2.21 (m, 2H, Ac_5c-$\beta CH \times 2$), 3.68 (s, 3H, OCH_3), 4.02 (d, 2H, J = 5.1, Gly-CH_2), 5.11 (s, 2H, Z-CH_2), 5.28 (s, 1H, Ac_5c-NH), 6.99 (br, 1H, Gly-NH), 7.3–7.4 (m, 15H, arom), 7.95 (s, 1H, Dph-NH)	24.2, 24.6 (Ac_5c-γC), 36.8 (Ac_5c-$\beta C \times 2$), 41.8 (Gly-αC), 52.2 (OCH_3), 67.1 (Z-CH_2), 67.6 (Ac_5c-αC), 70.2 (Dph-αC), 127.8, 128.0, 128.2, 128.3, 128.6, 136.1, 140.2 (arom), 155.6 (Z-C=O), 169.8, 171.6, 172.2 (C=O)
7h	Dph	Gly	58 38[e1] (EtOAc/ hexane)[2]	foamy solid		$C_{39}H_{35}N_3O_6$ (641.7)	3.65 (s, 3H, OCH_3), 3.88 (d, 2H, J = 5.1, Gly-CH_2), 4.96 (s, 2H, Z-CH_2), 6.27 (br, 1H, Gly-NH), 6.87 (s, 1H, Dph[1]-NH), 7.2–7.3 (m, 25H, arom), 7.86 (s, 1H, Dph[2]-NH)	41.8 (Gly-αC), 52.3 (OCH_3), 66.4 (Z-CH_2), 69.6 (Dph-αC), 70.3 (Dph-αC), 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 136.5, 138.1, 139.5 (arom), 154.1 (Z-C=O), 169.0, 169.4, 171.2 (C=O)

[a] Isolated yield by chromatography or recrystallization.
[b] For open column chromatography (1) or flash chromatography (2).
[c] For recrystallization.
[d] Satisfactory microanalyses obtained: C ± 0.25, H ± 0.21, N ± 0.29.
[e] Yield in the high pressure reaction at 0.9 GPa (9 kbar) for 14 d (e1), 7d (e2) or 10d (e3).

Table 2. Synthesis of Z-AA_1-Dph-AA_3-OMe **7i–r**

Product	AA_1	AA_3	Yield (%)[a] (Solvent)[b]	mp (°C) (Solvent)[c]	Molecular Formula[d]	^{1}H NMR ($CDCl_3$) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ
7i	Gly	Aib	16	141–142 (EtOAc/ hexane)	$C_{29}H_{31}N_3O_6$ (517.6)	1.45 (s, 6H, Aib-$\beta CH_3 \times 2$), 3.68 (s, 3H, OCH_3), 3.88 (d, 2H, J = 5.4, Gly-CH_2), 5.11 (s, 2H, Z-CH_2), 5.41 (br, 1H, Gly-NH), 6.42 (s, 1H, Aib-NH), 7.28–7.46 (m, 15H, arom), 7.90 (s, 1H, Dph-NH)	24.1 (Aib-$\beta C \times 2$), 44.9 (Gly-αC), 52.7 (OCH_3), 57.2 (Aib-αC), 67.0 (Z-CH_2), 70.2 (Dph-αC), 128.0, 128.08, 128.14, 128.3, 128.4, 128.47, 128.53, 136.2, 139.3 (arom), 156.4 (Z-C=O), 167.0, 170.5, 174.3 (C=O)
7j	Aib	Aib	35	172–173 (EtOAc/ hexane)	$C_{31}H_{35}N_3O_6$ (545.6)	1.47 (s, 6H, Aib-$\beta CH_3 \times 2$), 1.49 (s, 6H, Aib-$\beta CH_3 \times 2$), 3.65 (s, 3H, OCH_3), 5.08 (s, 2H, Z-CH_2), 5.42 (s, 1H, Aib[1]-NH), 6.85 (br, 1H, Aib[3]-NH), 7.2–7.4 (m, 15H, arom), 7.87 (s, 1H, Dph-NH)	24.3, 25.1 (Aib-$\beta C \times 4$), 52.4 (OCH_3), 56.9 (Aib-αC), 57.2 (Aib-αC), 66.7 (Z-CH_2), 69.8 (Dph-αC), 127.8, 128.0, 128.1, 128.2, 128.5, 136.2, 140.1 (arom), 155.1 (Z-C=O), 170.3, 172.2, 174.5 (C=O)
7k	Ac_3c	Aib	30	183–184 (EtOAc/ hexane)	$C_{31}H_{33}N_3O_6$ (543.6)	0.99 (dd, 2H, J = 7.5, 1.8, Ac_3c-$\beta CH \times 2$), 1.45 (s, 6H, Aib-$\beta CH_3 \times 2$), 1.49 (dd, 2H, J =7.5, 4.5, Ac_3c-$\beta CH \times 2$), 3.68 (s, 3H, OCH_3), 5.15 (s, 2H, Z-CH_2), 5.45 (s, 1H, Ac_3c-NH), 6.67 (br, 1H, Aib-NH), 7.3–7.4 (m, 15H, arom), 8.32 (s, 1H, Dph-NH)	17.4 (Ac_3c-$\beta C \times 2$), 24.3 (Aib-$\beta C \times 2$), 36.4 (Ac_3c-αC), 52.5 (OCH_3), 57.0 (Aib-αC), 67.3 (Z-CH_2), 70.3 (Dph-αC), 127.8, 128.2, 128.3, 128.6, 135.9, 139.9 (arom), 156.3 (Z-C=O), 170.0, 170.7, 174.4 (C=O)
7l	Ac_5c	Aib	56	174–175 (EtOAc)	$C_{33}H_{37}N_3O_6$ (571.7)	1.48 (s, 6H, Aib-$\beta CH_3 \times 2$), 1.71 (br, 4H, Ac_5c-$\gamma CH_2 \times 2$), 1.84 (br, 2H, Ac_5c-$\beta CH \times 2$), 2.22 (br, 2H, Ac_5c-$\beta CH \times 2$), 3.64 (s, 3H, OCH_3), 5.11 (s, 2H, Z-CH_2), 5.25 (s, 1H, Ac_5c-NH), 7.00 (br, 1H, Aib-NH), 7.2–7.4 (m, 15H, arom), 7.90 (s, 1H, Dph-NH)	24.3, 24.4 (Aib-$\beta C \times 2$, Ac_5c-$\gamma C \times 2$), 37.0 (Ac_5c-$\beta C \times 2$), 52.3 (OCH_3), 56.8, 67.6 (Aib-αC, Ac_5c-αC), 67.0 (Z-CH_2), 70.0 (Dph-αC), 127.7, 128.1, 128.2, 128.6, 136.0, 140.5 (arom), 155.5 (Z-C=O), 170.2, 172.0, 174.5 (C=O)

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Product	AA_1	AA_3	Yield (%)[a] (Solvent)[b]	mp (°C) (Solvent)[c]	Molecular Formula[d]	^{1}H NMR ($CDCl_3$) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ
7m	Dph	Aib	29 (EtOAc/ hexane)[2]	foamy solid	$C_{41}H_{39}N_3O_6$ (669.8)	1.36 (s, 6H, Aib-$CH_3 \times 2$), 3.58 (s, 3H, OCH_3), 4.95 (s, 2H, Z-CH_2), 6.40 (br, 1H, Aib-NH), 6.87 (s, 1H, Dph^1-NH), 7.1–7.4 (m, 25H, arom), 7.81 (s, 1H, Dph^2-NH)	24.1 (Aib-βC × 2), 52.5 (OCH_3), 56.9 (Aib-αC), 66.4 (Z-CH_2), 69.6 (Dph-αC), 70.2 (Dph-αC), 127.6, 127.7, 127.9, 128.0, 128.1, 128.15, 128.2, 128.3, 128.6, 128.8, 138.8, 139.6 (arom), 154.1 (Z-C=O), 169.0, 169.9, 174.3 (C=O)
7n	Gly	Ac_6c	18 (EtOAc/ hexane)[1]	foamy solid	$C_{32}H_{35}N_3O_6$ (557.7)	0.60–0.80 (m, 2H, Ac_6c-γCH_2), 1.02–1.18 (m, 1H, Ac_6c-δCH_2), 1.31–1.50 (m, 3H, Ac_6c-γCH_2, δCH_2), 1.61–1.74 (m, 2H, Ac_6c-βCH_2), 1.85–1.96 (m, 2H, βCH_2), 3.72 (s, 3H, OCH_3), 3.86 (d, J = 5.4, 1H, Gly-αCH_2), 5.10 (s, 2H, Z-CH_2), 5.39 (br, 1H, Gly-NH), 5.93 (s, 1H, Ac_6c-NH), 7.28–7.54 (m, 15H, arom), 7.95 (s, 1H, Dph-NH)	20.9 (Ac_6c-γC × 2), 24.7 (Ac_6c-δC), 31.8 (Ac_6c-βC × 2), 44.9 (Gly-αC), 52.4 (OCH_3), 59.3 (Ac_6c-αC), 67.0 (Z-CH_2), 70.2 (Dph-αC), 127.7, 127.9, 128.0, 128.03, 128.06, 128.12, 128.2, 128.3, 128.4, 136.2, 139.4 (Z-, Dph-arom), 156.4 (Z-C=O), 166.8, 170.4, 173.8 (C=O)
7o	Aib	Ac_6c	14	175–176 (EtOAc)	$C_{34}H_{39}N_3O_6$ (585.7)	0.84–1.05 (m, 2H, Ac_6c-γCH_2), 1.05–1.22 (m, 1H, Ac_6c-δCH_2), 1.38–1.56 (m, 9H, Ac_6c-γ, δCH_2, Aib-$\beta CH_3 \times 2$), 1.62–1.78 (m, 2H, Ac_6c-βCH_2), 1.92–2.05 (m, 2H, Ac_6c-βCH_2), 3.67 (s, 3H, OCH_3), 5.08 (s, 2H, Z-CH_2), 5.43 (br, 1H, Aib-NH), 6.40 (br, 1H, Ac_6c-NH), 7.27–7.52 (m, 15H, arom), 8.04 (s, 1H, Dph-NH)	21.0 (Ac_6c-γC × 2), 24.9 (Ac_6c-δC), 25.1 (Aib-βC × 2), 31.9 (Ac_6c-βC × 2), 52.1 (OCH_3), 57.2 (Aib-αC), 59.3 (Ac_6c-αC), 66.6 (Z-CH_2), 70.1 (Dph-αC), 127.9, 128.0, 128.1, 128.3, 128.5, 136.2, 140.0 (Z-, Dph-arom), 154.9 (Z-C=O), 170.5, 172.2, 174.0 (C=O)
7p	Ac_3c	Ac_6c	39 50[e]	188–190 (EtOAc)	$C_{34}H_{37}N_3O_6$ (583.7)	0.79–0.95 (m, 2H, Ac_6c-γCH_2), 0.95–1.04 (m, 2H, Ac_3c-βCH_2), 1.04–1.21 (m, 1H, Ac_6c-δCH_2), 1.36–1.53 (m, 5H, Ac_3c-βCH_2, Ac_6c-γCH_2, δCH_2), 1.62–1.75 (m, 2H, Ac_6c-$\beta CH \times 2$), 1.89–2.01 (m, 2H, Ac_6c-$\beta CH_2 \times 2$), 3.70 (s, 3H, OCH_3), 5.14 (s, 2H, Z-CH_2), 5.43 (br, 1H, Ac_3c-NH), 6.40 (br, 1H, Ac_6c-NH), 7.25–7.53 (m, 15H, arom), 8.37 (Dph-NH)	17.5 (Ac_3c-βC × 2), 21.0 (Ac_6c-γC × 2), 24.8 (Ac_6c-δC), 31.9 (Ac_6c-βC × 2), 36.4 (Ac_3c-αC), 52.1 (OCH_3), 59.2 (Ac_6c-δC), 67.3 (Z-CH_2), 70.4 (Dph-αC), 127.89, 127.92, 127.95, 128.4, 128.53, 128.56, 128.6, 128.7, 135.9, 140.0 (arom), 156.3 (Z-C=O), 170.0, 170.7, 174.1 (C=O)
7q	Ac_6c	Ac_6c	8 6[e]	148–149 (EtOAc/ hexane)	$C_{37}H_{43}N_3O_6$ (625.8)	1.00–1.65 (m, 12H, Ac_6c-$\gamma CH_2 \times 4$, $\delta CH_2 \times 2$), 1.65–1.84 (m, 4H, Ac_6c-$\beta CH \times 4$), 1.92–2.10 (m, 4H, Ac_6c-$\beta CH \times 4$), 3.64 (s, 3H, OCH_3), 5.07 (s, 1H, Ac_6c^1-NH), 5.12 (s, H, Z-CH_2), 6.78 (s, 1H, Ac_6c^3-NH), 7.26–7.46 (m, 15H, arom), 8.03 (s, 1H, Dph-NH)	21.23, 21.28 (Ac_6c-γC × 4), 24.97, 25.01 (Ac_6c-δC × 2), 31.83, 31.95 (Ac_6c-βC × 4), 51.9 (OCH_3), 59.2, 60.1 (Ac_6c-αC × 2), 67.0 (Z-CH_2), 70.1 (Dph-αC), 127.7, 127.74, 127.8, 128.2, 128.47, 128.50, 128.57, 128.6, 136.1, 140.5 (arom), 155.0 (Z-C=O), 170.4, 172.5, 174.2 (C=O)
7r	Dph	Ac_6c	10 (EtOAc/ hexane)[2]	oil	$C_{44}H_{43}N_3O_6$ (709.8)	0.56–0.74 (m, 2H, Ac_6c-γCH_2), 1.02–1.10 (m, 1H, Ac_6c-δCH_2), 1.32–1.44 (m, 2H, Ac_6c-γCH_2), 1.54–1.68 (m, 3H, Ac_6c-βCH_2, -δCH_2), 1.74–1.84 (m, 2H, Ac_6c-βCH_2), 3.61 (s, 3H, OCH_3), 4.93 (s, 2H, Z-CH_2), 5.76 (s, 1H, Ac_6c-NH), 6.94 (s, 1H, Dph^1-NH), 7.19–7.41 (m, 25H, arom), 7.85 (s, 1H, Dph^2-NH)	20.9 (Ac_6c-γC × 2), 24.7 (Ac_6c-δC), 31.7 (Ac_6c-βC × 2), 52.2 (OCH_3), 59.2 (Ac_6c-αC), 66.3 (Z-CH_2), 69.6, 70.3 (Dph-αC), 127.0, 127.68, 127.72, 127.9, 128.00, 128.03, 128.1, 128.17, 128.23, 128.3, 128.4, 128.66, 128.72, 138.7, 139.4 (arom), 153.9 (Z-C=O), 169.0, 169.9, 173.7 (C=O)

[a] Isolated yield by chromatography or recrystallization.
[b] For open column chromatography (1), flash chromatography (2) or preparative TLC (3).
[c] For recrystallization.
[d] Satisfactory microanalyses obtained: C ± 0.26, H ± 0.16, N ± 0.13.
[e] Yield in the high pressure reaction at 0.9 GPa (9 kbar) for 14 d.

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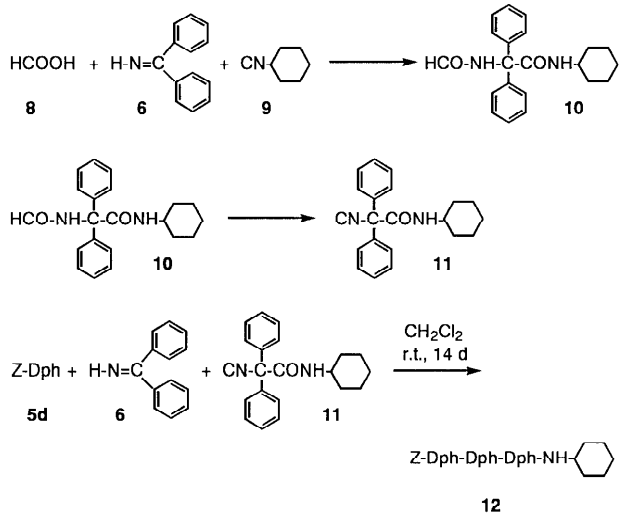

also obtained under atmospheric pressure, though in a lower yield.

In conclusion, we could clarify that the modified Ugi reaction using the Schiff's base **6**, as a key compound is very useful and potent for synthesis of various crowded peptides containing α,α-diphenylglycine (Dph) together with very bulky α,α-disubstituted glycines.

Mps were obtained on a Yamato melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian UNITY 300 spectrometer. IR spectra were obtained on a JASCO IR-810 spectrophotometer. Optical rotations were recorded on a JASCO DIP-4 digital polarimeter. Most of reagents and solvents were purchased from Wako Pure Chemical Industries, Ltd. and Tokyo Kasei Kogyo Co. and used without further purification. Dph, Ac_5c, Ac_6c and triphosgen were purchased from Aldrich Chemical Co. and diphosgen from Hodogaya Chemical Co. Methyl isocyanoacetate,[10] cyclohexyl isocyanide,[10, 12] and Ac_3c[13] were prepared by the literature method. TLC analysis was performed on Merck precoated silica gel glass plates (type G_{60}-F_{254}). Products were isolated by flash column chromatography on silica gel (Wakogel FC-40, Wako Pure Chemical Industries, Ltd.) or by open column chromatography (Wakogel C-300, Wako Pure Chemical Industries, Ltd.). Reactions at high pressure at 9 kbar (0.9 GPa) were carried out by using a stainless steel apparatus for high pressure reaction made by Hikari Kogyo Ltd.

Methyl 2-Isocyano-2-methylpropionate (4b):

HCO-Aib-OMe **(3b)**:

To a solution of HCO-Aib[14] **(2b)** (13.1 g, 0.1 mol) in EtOH (300 mL) was added a solution of freshly prepared diazomethane in Et_2O. Then to the mixture was added a small amount of AcOH in order to decompose excess diazomethane and the solution was concentrated under reduced pressure. The crude product was distilled in vacuo, affording a colorless oil; yield: 14.2 g (98%); bp 91–93 °C/0.6–0.7 Torr.

$C_6H_{11}NO_3$	calcd	C	49.65	H	7.64	N	9.65
(145.16)	found		49.58		7.71		9.60

^{1}H NMR ($CDCl_3$): δ (*trans*/*cis*) = 1.55/1.57 (s, 6H, Aib-$CH_3 \times 2$), 3.75/3.74 (s, 3H, OCH_3), 6.38 (br, 1H, NH), 8.07/8.24 (d, 1H, J = 1.5/12.3 Hz, HCO), (*trans*/*cis* 6:1).

Conversion of **3b** *to* **4b**:

While a cold solution of **3b** (11.7 g, 0.08 mol) and Et_3N (16.2 g, 0.16 mol) in CH_2Cl_2 (150 mL) was stirred below –10 °C using an ice-salt bath, a solution of diphosgen (4.5 mL, 0.04 mol) in CH_2Cl_2 (30 mL) was added dropwise over 15 min. After stirring for 30 min at the same temperature and then for 1 h at r.t., the resulting Et_3N·HCl was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc (100 mL), and the solution was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was distilled in vacuo to give a colorless oil; yield: 6.57 g (64%); bp 48–51 °C/2 Torr.

$C_6H_9NO_2$	calcd	C	56.68	H	7.13	N	11.02
(127.14)	found		56.50		7.09		10.73

IR (neat): ν = 1752 (C=O), 2144 cm^{-1} (-NC).
^{1}H NMR ($CDCl_3$): δ = 1.63 (s, 6H, $\beta CH_3 \times 2$), 3.79 (s, 3H, OCH_3).
^{13}C NMR ($CDCl_3$): δ = 27.5 ($\beta C \times 2$), 53.5 (OCH_3), 59.5 (αC), 157.8 (NC), 170.0 (C=O).

Methyl 1-Isocyanocyclohexane-1-carboxylate (4c):

HCO-Ac_6c **(2c)**:

To a solution of Ac_6c (14.32 g, 100 mmol) in 98% HCO_2H (250 mL) was added Ac_2O (10 mL) drop by drop at 60 °C under stirring. After stirring for 3.5 h, to the mixture was added ice-water (10 mL) and the mixture was concentrated under reduced pressure, affording white crystals. The crude product was suspended in Et_2O and filtered after vigorous stirring, to give pure HCO-Dph; yield: 16.1 g (94%); mp 179–184 °C (dec).

$C_8H_{13}NO_3$	calcd	C	56.13	H	7.65	N	8.18
(171.2)	found		56.08		7.89		8.20

^{1}H NMR (DMSO-d_6): δ (*trans*/*cis*) = 1.10–1.25 (m, 1H, Ac_6c-δCH_2), 1.29–1.54 (m, 5H, Ac_6c-$\gamma CH_2 \times 2$, -δCH_2), 1.54–1.68 (m, 2H, Ac_6c-βCH_2), 1.74–1.96 (m, 2H, Ac_6c-βCH_2), 7.90/8.11 (d, 1H, J = 1.5/11.7 Hz, HCO), 8.14 (br, 1H, Ac_6c-NH) (*trans*/*cis* 6:1).

HCO-Ac_6c-OMe **(3c)**:

To a solution of **2c** (5.00 g, 29 mmol) in Et_2O (20 mL) and $CHCl_3$ (5 mL) was added a solution of freshly prepared diazomethane in Et_2O. After 1 d, to the mixture was added a small amount of AcOH in order to decompose excess diazomethane and the solution was concentrated under reduced pressure, to give a white solid. The crude product was recrystallized (EtOAc/*n*-hexane), affording white crystals; yield: 4.72 g (87%); mp 104–105 °C.

$C_9H_{15}NO_3$	calcd	C	58.36	H	8.16	N	7.56
(185.2)	found		58.11		8.19		7.55

^{1}H NMR ($CDCl_3$): δ (*trans*/*cis*) = 1.24–1.40 (m, 1H, Ac_6c-δCH_2), 1.40–1.54 (m, 2H, Ac_6c-γCH_2), 1.54–1.61 (m, 1H, Ac_6c-δCH_2), 1.61–1.72 (m, 2H, Ac_6c-γCH_2), 1.80–1.92 (m, 2H, Ac_6c-βCH_2), 2.11 (m, 2H, Ac_6c-βCH_2), 3.72/3.76 (s, 3H, OCH_3), 6.37 (br, 1H, Ac_6c-NH), 8.13/8.26 (d, 1H, J = 1.2/12.3 Hz, HCO), (*trans*/*cis* 4:1).
^{13}C NMR ($CDCl_3$): δ = 20.88, 21.23 (Ac_6c-$\gamma C \times 2$), 24.75, 25.00 (Ac_6c-δC), 32.28, 33.74 (Ac_6c-$\beta C \times 2$), 52.4, 52.8 (OCH_3), 58.5, 59.1 (Ac_6c-αC), 160.8, 164.3 (HCO), 174.0, 174.2 (Ac_6c-C=O).

Conversion of HCO-Ac_6c-OMe **(3c)** *to* **4c**:

While a cold solution of **3c** (4.83 g, 26 mmol) and Et_3N (8.0 g, 79 mmol) in CH_2Cl_2 (84 mL) was stirred below –10 °C using ice-salt bath, a solution of triphosgen (2.55 g, 8.6 mmol) in CH_2Cl_2 (25 mL) was added dropwise over 15 min. After stirring for 5 min at the same temperature and then for 4 h at r.t., the resulting Et_3N•HCl was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL), and the solution was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by distillation in vacuo to give a colorless oil; yield: 3.03 g (69.5%), bp 45–50 °C/0.4 Torr.

$C_9H_{13}NO_2$	calcd	C	64.65	H	7.84	N	8.38
(167.21)	found		64.81		7.77		8.42

IR (neat): ν = 1750 (C=O), 2140 cm^{-1} (-NC).
^{1}H NMR ($CDCl_3$): δ = 1.15–1.35 (m, 1H, Ac_6c-δCH_2), 1.57–1.77 (m, 5H, Ac_6c-$\gamma CH_2 \times 2$, -δCH_2), 1.77–1.90 (m, 2H, Ac_6c-βCH_2), 1.95–2.05 (m, 2H, Ac_6c-βCH_2), 3.81 (s, 3H, OCH_3).

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Table 3. Synthesis of Z-AA_1-Dph-Dph-OMe **7s–v** and Z-Dph-Dph-Dph-NHcHex (**14**)

Product	AA_1	AA_3	Yield (%)[a] (Solvent)[b]	mp (°C) (Solvent)[c]	Molecular Formula[d]	^{1}H NMR ($CDCl_3$) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ
7s	Aib	Dph	41[e2]	181–182 (EtOAc/ hexane)	$C_{41}H_{39}N_3O_6$ (669.8)	1.43 (s, 6H, Aib-$CH_3 \times 2$), 3.61 (s, 3H, OCH_3), 4.99 (s, 2H, Z-CH_2), 5.42 (br, 1H, Aib-NH), 7.19–7.37 (m, 25H, arom), 7.63 (s, 1H, Dph^3-NH), 8.07 (s, 1H, Dph^2-NH)	25.0 (Aib-βC × 2), 53.4 (OCH_3), 57.1 (Aib-αC), 66.5 (Z-CH_2), 69.7, 70.0 (Dph-αC), 127.66, 127.72, 127.86, 127.9, 128.0, 128.1, 128.3, 136.3, 137.4, 137.8, 139.4 (arom), 154.8 (Z-C=O), 169.4, 171.8, 171.9 (C=O)
7t	Ac_3c	Dph	10[e1]	188–190 (EtOAc/ hexane)	$C_{41}H_{37}N_3O_6$ (667.8)	0.92–0.99, 1.43–1.50 (m, 4H, Ac_3c-$\beta CH_2 \times 2$), 3.64 (s, 3H, OCH_3), 5.06 (s, 2H, Z-CH_2), 5.29 (br, 1H, Ac_3c-NH), 7.17–7.37 (m, 25H, arom), 7.61 (s, 1H, Dph^3-NH), 8.38 (s, 1H, Dph^2-NH)	17.2 (Ac_3c-βC × 2), 36.3, (Ac_3c-αC), 53.5 (OCH_3), 66.2 (Z-CH_2), 69.9, 70.0 (Dph-αC), 127.6, 127.8, 127.86, 127.89, 128.0, 128.1, 128.15, 128.3, 128.4, 128.5, 135.8, 137.9, 139.5 (arom), 156.1 (Z-C=O), 169.5, 171.8, 175.6 (C=O)
7u	Ac_6c	Dph	9[e1] (EtOAc/ hexane)	oil	$C_{44}H_{43}N_3O_6$ (709.8)	1.14–1.22 (m, 1H, Ac_6c-δCH_2), 1.22–1.38 (m, 2H, Ac_6c-γCH_2), 1.50–1.62 (m, 3H, Ac_6c-γ, δCH_2), 1.66–1.79 (m, 2H, Ac_6c-βCH_2), 1.88–2.00 (m, 2H, Ac_6c-βCH_2), 3.61 (s, 3H, OCH_3), 4.97 (s, 1H, Ac_6c-NH), 5.01 (s, 2H, Z-CH_2), 7.16–7.4 (m, 25H, arom), 7.82 (br, 1H, Dph^3-NH), 8.16 (s, 1H, Dph^2-NH)	21.1 (Ac_6c-γC × 2), 25.0 (Ac_6c-δC), 31.6 (Ac_6c-βC × 2), 53.2 (OCH_3), 60.0 (Ac_6C-αC), 66.9 (Z-CH_2), 69.8, 69.9 (Dph-αC), 127.77, 127.82, 127.9, 128.0, 128.2, 128.27, 128.32, 128.4, 128.8, 128.87, 128.9, 129.0, 136.1, 138.2, 140.0 (arom), 154.9 (Z-C=O), 169.5, 171.8, 172.3 (C=O)
7v	Dph	Dph	12[e3]	219–220 (EtOAc)	$C_{51}H_{43}N_3O_6$ (793.9)	3.56 (s, 3H, OCH_3), 4.90 (s, 2H, Z-CH_2), 6.92 (s, 1H, Dph^1-NH), 7.04–7.09, 7.22–7.30 (m, 36H, arom and Dph-NH), 7.76 (s, 1H, Dph-NH)	53.4 (OCH_3), 66.2 (Z-CH_2), 69.5, 69.8, 70.2 (Dph-αC), 127.76, 127.83, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 137.6, 138.4, 139.2 (arom), 153.8 (Z-C=O), 168.6, 168.9, 171.7 (C=O)
14	Dph	Dph	15 43[e1]	188–189 (EtOAc/ PE)	$C_{56}H_{52}N_4O_5$ (861.1)	0.8–1.6 (m, 10H, cHex-$CH_2 \times 5$), 3.56 (m, 1H, cHex-CH), 4.90 (s, 2H, Z-CH_2), 5.42 (br, 1H, cHex-NH), 6.93 (s, 1H, Dph^1-NH), 7.0–7.3 (m, 35H, arom), 7.74 (s, 1H, Dph-NH), 7.83 (s, 1H, Dph-NH)	24.3 (cHex-3,6-C), 25.2 (cHex-4-C), 32.1 (cHex-2,5-C), 48.9 (cHex-1-C), 66.2 (Z-CH_2), 69.6, 70.0, 70.2 (Dph-αC), 127.6, 127.7, 127.8, 128.0, 128.15, 128.2, 128.4, 128.5, 128.7,128.8, 136.6, 138.5, 139.3 (arom), 153.8 (Z-C=O), 168.3, 169.0, 169.7 (C=O)

[a] Isolated yield by chromatography or recrystallization.
[b] preparative TLC.
[c] For recrystallization.
[d] Satisfactory microanalyses obtained: C ± 0.26, H ± 0.16, N ± 0.06.
[e] Yield in the high pressure reaction at 0.9 GPa (9 kbar) for 14 d (e1), 10 d (e2) or 17 d (e3).

^{13}C NMR ($CDCl_3$): δ = 20.8 (Ac_6c-γC × 2), 24.3 (Ac_6c-δC), 34.3 (Ac_6c-βC × 2), 53.3 (OCH_3), 64.3 (Ac_6c-αC), 158.8 (NC), 170.0 (Ac_6c-C=O).

Methyl 2-Isocyano-2,2-diphenylacetate (4d):

HCO-Dph **(2d)**:

To a solution of Dph (4.54 g, 20 mmol) in 90% HCO_2H (50 mL) was added Ac_2O (20 mL) drop by drop at 60 °C under stirring. After stirring for 3 h, to the mixture was added ice-water (5 mL) and the mixture was concentrated under reduced pressure, affording a white solid. The crude product was suspended in 50% aq AcOH and filtered after vigorous stirring, to give pure HCO-Dph ; yield: 4.41 g (86%); mp 200 °C (dec).

$C_{15}H_{13}NO_3$ (255.3)	calcd	C	70.58	H	5.13	N	5.49
	found		70.55		5.12		5.53

^{1}H NMR (DMSO-d_6): δ (*trans*/*cis*) = 7.2–7.4 (m, 10H, Dph-arom), 8.15/7.77 (d, 1H, J = 1.5/12.3 Hz, HCO), 9.25 (br, 1H, NH) (*trans*/*cis* 95:5).

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HCO-Dph-OMe **(3d)**:
To a solution of **2d** (4.47 g, 17.5 mmol) in MeOH (100 mL) was added a solution of freshly prepared diazomethane in Et_2O. Then to the mixture was added a small amount of AcOH in order to decompose excess diazomethane and the solution was concentrated under reduced pressure, to give a white solid. The crude product was recrystallized (EtOAc), affording white crystals; yield: 4.52 g (85%); mp 146–147°C.

$C_{16}H_{15}NO_3$	calcd	C	71.36	H	5.61	N	5.20
(269.3)	found		71.55		5.76		5.44

^{1}H NMR ($CDCl_3$): δ (*trans*/*cis*) = 3.77/3.81 (s, 3H, OCH_3), 7.21 (d, 0.6H, *J* = 12 Hz (*cis*), NH), 7.25–7.5 (m, 10.4H, Dph-arom and NH), 8.25/7.78 (d, 1H, *J* = 1.5/12.3 Hz, HCO), (*trans*/*cis* 2:3).
^{1}H NMR (DMSO-d_6): δ (*trans*/*cis*) = 3.66/3.75 (s, 3H, OCH_3), 7.2–7.4 (m, 10H, arom), 8.14/7.77 (d, 1H, *J* = 1.5/12 Hz, NH), 9.25/8.70 (d, 1H, *J* = 1.5/12 Hz, HCO), (*trans*/*cis* 94:6).
^{13}C NMR ($CDCl_3$): δ (*trans*/*cis*) = 53.6/53.7 (OCH_3), 69.7/69.9 (Dph-αC), 128.0/128.3, 128.4/128.7, 138.2/139.3 (Dph-arom), 159.2/164.8 (HCO), 172.3/ 171.9 (Dph-C=O).

Conversion of HCO-Dph-OMe **(3d)** *to* **4d**:
While a cold solution of **3d** (808 mg, 3 mmol) and Et_3N (607 mg, 6 mmol) in CH_2Cl_2 (30 mL) was stirred below –10°C using an ice-salt bath, a solution of diphosgen (0.16 mL, 1.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 15 min. After stirring for 30 min at the same temperature and then for 2 h at r.t., the resulting $Et_3N{\bullet}HCl$ was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc (20 mL), and the solution was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Wakogel FC-40, hexane/EtOAc 2:1) to give white solid, which was recrystallized (EtOAc); yield: 657 mg (65%), mp 66–68°C.

$C_{16}H_{13}NO_2$	calcd	C	76.48	H	5.21	N	5.57
(251.3)	found		76.70		5.18		5.50

IR (KBr): ν = 1748 (C=O), 2138 cm^{-1} (-NC).
^{1}H NMR ($CDCl_3$): δ = 3.89 (s, 3H, OCH_3), 7.41 (s, 10H, arom).
^{13}C NMR ($CDCl_3$): δ = 54.1 (OCH_3), 69.0 (αC), 127.2, 128.7, 129.1, 137.0 (arom), 161.6 (NC), 167.8 (C=O).

Synthesis of Dph-Containing Peptides:

Z-AA$_1$-Dph-AA$_3$-OMe 7a–w; General Procedure:

Method A (Atmospheric Pressure):
A solution of *N*-Z-amino acid **5** (11 mmol), diphenylmethanimine **(6)**[5] (2.00 g, 11 mmol), and isocyanides **4a–d** (10 mmol) in CH_2Cl_2 (10 mL) was stirred at r.t. for 14 d. In the case of the reaction of Z-Ac$_5$c, MeOH was used as a solvent because Z-Ac$_5$c hardly dissolves in CH_2Cl_2. The solvent was removed under vacuum, and the residue was dissolved in EtOAc (400 mL). This solution was washed with 1 M HCl (2 × 50 mL), 1 M $NaHCO_3$ (2 × 50 mL) and H_2O (2 × 50 mL), and dried (Na_2SO_4). The solvent was evaporated and the crude product was purified by flash chromatography or open column chromatography using the eluents given in Tables, and/or by recrystallization. Results are summarized in Tables 1–3.

Method B (High Pressure):
A mixture of *N*-Z-amino acid (4.4 mmol), **6** (797 mg, 4.4 mmol), and isocyanides **4a**, **4c,** and **4d** (4.04 mmol) was dissolved in CH_2Cl_2 (2.1–2.5 mL) in a Teflon capsule (4.5 mL capacity). The solution was compressed at 0.9 GPa (9 kbar) by the use of a stainless steel apparatus for 7–14 d. The mixture was concentrated under vacuum, and the residue was dissolved in EtOAc (200 mL). The solution was washed with 1 M HCl (2 × 30 mL), 1 M $NaHCO_3$ (2 × 30 mL) and H_2O (2 × 30 mL), and dried (Na_2SO_4). The solvent was removed and the crude product was purified by flash chromatography using the eluents given in Tables. Results are summarized in Tables 1–3.

Z-Dph-Dph-Dph-NHcHex (12):

HCO-Dph-NHcHex **(10)**:
A solution of HCO_2H (1.52 g, 33 mmol), diphenylmethanimine **(6)**[5] (9.80 g, 36 mmol), and cyclohexyl isocyanide **(9)** (3.28 g, 30 mmol) in CH_2Cl_2 (30 mL) was stirred at r.t. for 12 d. A precipitate formed during the reaction was filtered and the crude product (11.1 g) was recrystallized (EtOAc), affording white crystals (7.69 g). The filtrate was concentrated under reduced pressure and the residue was also recrystallized (EtOAc), giving some white crystals (0.85 g). Total yield: 8.54 g (85%); mp 188–190°C.

$C_{21}H_{24}N_2O_2$	calcd	C	74.97	H	7.19	N	8.33
(336.4)	found		75.03		7.23		8.30

^{1}H NMR ($CDCl_3$): δ (*trans*/*cis*) = 0.9–1.16 (m, 3H, cHex-2,6-H$_{ax}$ and 4-H$_{ax}$), 1.22–1.4 (m, 2H, cHex-3,5-H$_{ax}$), 1.45–1.62 (m, 3H, cHex-3,5-H$_{eq}$ and 4-H$_{eq}$), 1.7–1.86 (m, 2H, cHex-2,6-H$_{eq}$), 3.7–3.87 (m, 1H, cHex-1-H), 5.46/5.31 (d, 1H, *J* = 8 Hz, -NH-cHex), 7.28–7.53 (m, 10H, arom), 7.79/7.53 (br/d, 1H, *J* = 12 Hz (*cis*), Dph-NH), 8.22/7.87 (d, 1H, *J* = 1.2/12 Hz, HCO), (*trans*/*cis* 3:2).
^{13}C NMR ($CDCl_3$): δ (*trans*/*cis*) = 24.3/24.4 (cHex-3,5-C), 25.2 (cHex-4-C), 32.2/32.4 (cHex-2,6-C), 49.1/49.2 (cHex-1-C), 70.0/69.8 (Dph-αC), 128.1, 128.3, 128.4, 128.8, 129.0, 139.4/139.9 (arom), 159.2/164.4 (HCO), 170.4/169.9 (Dph-C=O).

Conversion of HCO-Dph-NHcHex **(10)** *to N-Cyclohexyl-2-isocyano-2,2-diphenylacetamide* **(11)**:
While a cold solution of **10** (2.02 g, 6 mmol) and Et_3N (1.01 g, 12 mmol) in CH_2Cl_2 (40 mL) was stirred below –10°C using ice-salt bath, a solution of triphosgen (600 mg, 3 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 15 min. After stirring for 30 min at the same temperature and then for 3 h at r.t., the resulting $Et_3N{\bullet}HCl$ was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc (30 mL), and the solution was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Wakogel FC-40, hexane/EtOAc 5:1) to give white crystals; yield: 782 mg (41%); mp 113–114°C.

$C_{21}H_{22}N_2O$	calcd	C	79.21	H	6.96	N	8.80
(318.4)	found		79.11		7.04		8.87

IR (KBr): ν = 1665 (C=O), 2128 cm^{-1} (-NC).
^{1}H NMR ($CDCl_3$): δ = 1.1–1.5 (m, 5H, cHex-2,6-, 3,5- and 4-H$_{ax}$), 1.55–1.8 (m, 3H, cHex-3,5- and 4-H$_{eq}$), 1.9–2.0 (m, 2H, cHex-2,6-H$_{eq}$), 3.82 (m, 1H, cHex-1-H), 6.55 (br, 1H, *J* = 8.4 Hz, NH), 7.3–7.45 (m, 10H, arom).
^{13}C NMR ($CDCl_3$): δ = 24.6, 25.3, 32.6, 49.5, 59.3 (cHex), 74.0 (Dph-αC), 127.3, 128.5, 128.8, 137.8 (arom), 161.3 (NC), 164.9 (C=O).

Z-Dph-Dph-Dph-NHcHex **(12)**:
Method A (Atmospheric Pressure):
A mixture of *N*-Z-Dph **(5d)** (400 mg, 1.1 mmol), **6** (270 mg, 1.5 mmol) and the isocyanide **11** (130 mg, 0.4 mmol) was dissolved in CH_2Cl_2 (2 mL), and was stirred for 14 d at r.t. The mixture was concentrated under vacuum, and the residue was dissolved in EtOAc (20 mL). The solution was washed with 1 M HCl (2 × 5 mL), 1 M $NaHCO_3$ (2 × 5 mL) and H_2O (3 × 5 mL), and dried (Na_2SO_4). Removal of solvent afforded a crude product, which was purified by preparative TLC, affording white crystals. The crude crystals were recrystallized (EtOAc/petroleum ether); yield: 50 mg (14.5%); mp 188–189°C.

Method B (High Pressure):
A mixture of *N*-Z-Dph **(5d)** (400 mg, 1.1 mmol), **6** (270 mg, 1.5 mmol), and **11** (320 mg, 1.0 mmol) was dissolved in CH_2Cl_2 (4 mL) in a Teflon capsule (4.5 mL capacity). The solution was com-

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pressed at 0.9 GPa (9 kbar) by the use of a stainless steel apparatus for 14 d at r.t. The mixture was concentrated under vacuum, and the residue was dissolved in EtOAc (20 mL). The solution was washed with 1 M HCl (2 × 5 mL), 1 M $NaHCO_3$ (2 × 5 mL), and H_2O (3 × 5 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure. The resulting crude product was purified by flash column chromatography (Wakogel FC-40, hexane/EtOAc 4:1), affording white crystals, which were recrystallized (EtOAc/petroleum ether); yield: 421 mg (49%); mp 188–189°C. Spectral data are given in Table 3.

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