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Sodium Borohydride Reduction of Carbamoyl Azide Function: A Synthesis of *N*-Protected *N*′-Formyl-*gem*-diaminoalkyl Derivatives

Giancarlo Verardo*[a] and Andrea Gorassini[b]

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A simple, efficient two-step synthesis of *N*-protected *N*′-formyl-*gem*-diaminoalkyl derivatives is reported. The procedure involves the unprecedented reduction of the carbamoyl azide of α-*N*-Boc/Fmoc/Z-protected amino acids and dipeptides (Boc = *tert*-butoxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl, Z = benzyloxycarbonyl) by treatment with $NaBH_4$ at room temperature. The reaction proceeds rapidly (45 min) without detectable epimerization (by HPLC-ESI-MS analysis) and is not influenced by the nature of the starting carbamoyl azide. The ^1H and ^{13}C NMR analyses of the synthesized *N*-protected *N*′-formamides were carried out in [D_6]DMSO. The spectra exhibited the presence of two rotameric forms in solution as a result of the restricted rotation around the N–CO formyl bond. The integration of the N–CH–N protons of the two isomers showed that the *cis* isomer (rotamer B) was the more abundant conformer by 60 to 78 %. The reported synthesis represents the potential value of carbamoyl azides as versatile chiral starting materials for many synthetic purposes.

Introduction

Compounds that contain the *N*-formyl moiety are important derivatives and are employed as anti-inflammatory,[1] anticancer,[1,2] immunogenic,[3] and antibacterial[4] agents. Moreover, they have wide applications to heterocyclic[5] pharmaceuticals and organic synthesis. For example, formamides are used as a catalyst in the enantioselective hydrosilylation of C=N[6] and C=O[6i,6n,7] bonds as well as in the asymmetric allylation[8] of carbonyl compounds. Furthermore, they are useful starting materials in the syntheses of isocyanides,[5a,9] formamidines,[10] *N*-monomethylamines,[11] and Vilsmeier reagents.[12] The formyl group is also employed to protect the amino group in peptide synthesis.[13]

A number of *N*-formylation methods have been reported in recent years, and some of these can also be applied to the amino group of α-amino acid derivatives. These include the direct reaction of formic acid in the presence of ionic liquids[14] or thiamine hydrochloride[15] or the employment of activated formic acid by using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI).[16] Many other useful formylating reagents have been reported such as formic acid esters,[17] ammonium formate,[18] trimethyl orthoformate,[19] *N*-(diethylcarbamoyl)-*N*-methoxyformamide,[20] and *N*,*N*-dimethylformamide in the presence of imidazole.[21] However, only two reports[22] describe the conversion of the carboxyl component of *N*-protected amino acids into the corresponding formamide (see Figure 1) with the retention of configuration. These derivatives represent an interesting alternative to the unstable asymmetric *N*-protected *gem*-diamines[23] that are particularly useful to the synthesis of partially modified retro-inverso peptides.[24]

Figure 1. Conversion of *N*-protected amino acid into corresponding formamide (PG = protecting group).

According to the most common procedure for the preparation of *N*,*N*′-diurethane *gem*-diamines, the synthesis of these formamides involves a Curtius rearrangement to convert the *N*-formyl protected α-amino acid azide into the corresponding isocyanate. The subsequent alcoholysis of the obtained isocyanate affords the corresponding *N*-formyl-*N*′-alkoxycarbonyl *gem*-diamine[13f] (see Scheme 1, Route A). Sureshbabu and co-workers[22] have proposed an alternative approach (see Scheme 1, Route B) by treating the *N*-protected α-amino isocyanate with formic acid in the presence of 4-dimethylaminopyridine (DMAP).

Recently, we reported the preparation of the carbamoyl azides of α-*N*-protected amino acids,[25] and by studying their reactivity,[26] we realized that this functional group can

[a] Department of Chemical Sciences and Technologies, University of Udine,
Via del Cotonificio 108, 33100 Udine, Italy
Fax: +39-0432-558803
E-mail: giancarlo.verardo@uniud.it
Homepage: http://www.uniud.it
[b] Dipartimento di Storia e Tutela dei Beni Culturali, University of Udine,
Palazzo Caiselli, Vicolo Florio 2, 33100 Udine, Italy
E-mail: andrea.gorassini@uniud.it

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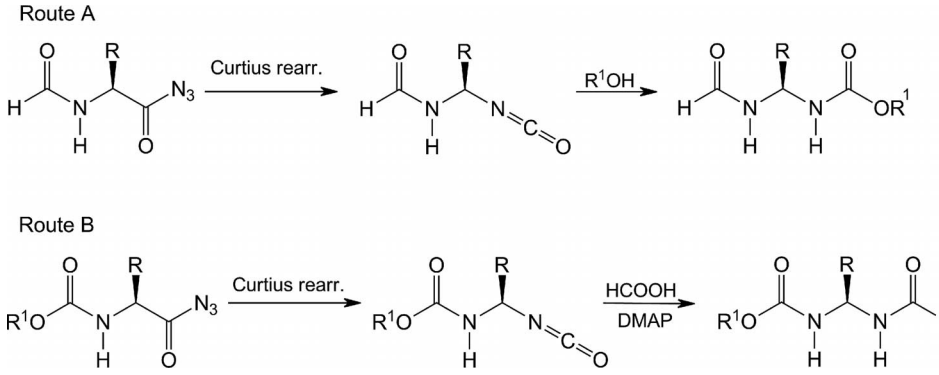
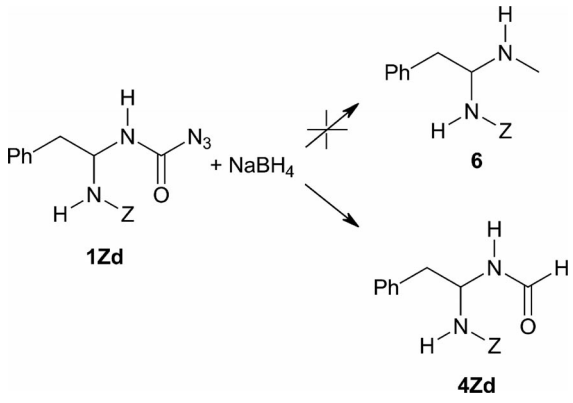


Scheme 1. General approaches to the synthesis of *N*-formyl-*N*′-protected asymmetric *gem*-diamines.

be considered a –N=C=O equivalent. Taking into account this acquired experience and that some authors have reported the direct reduction of aryl and alkyl isocyanates into the corresponding formamides[27] or *N*-methylamines,[27a,28] we now report our study of the reduction of the carbamoyl azide moiety with $NaBH_4$.

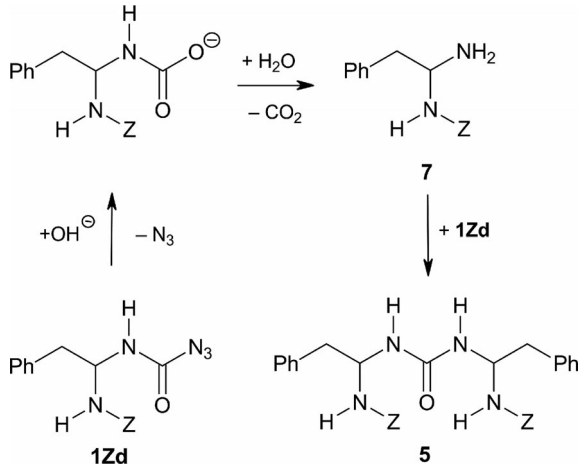
Results and Discussion

In the present study, the carbamoyl azide of α-*N*-benzyloxycarbonylphenylalanine (**1Zd**), which was obtained from Z-Phe-OH (**2Zd**, Z = benzyloxycarbonyl) through the corresponding mixed anhydride **3Zd** in the presence of a buffered aqueous solution (KH_2PO_4/K_2HPO_4, pH ≈ 7) of NaN_3,[26] was used as the model substrate. The first approach involved the addition of powdered $NaBH_4$ (3.5 equiv.) directly to the well-stirred final tetrahydrofuran (THF)/water buffer biphasic mixture that contained the prepared carbamoyl azide **1Zd** (1.0 equiv.) at room temperature. The ESI-MS analysis of the intact reaction mixture showed the complete disappearance of **1Zd** after 3 h and the formation of the corresponding *N*-benzyloxycarbonyl-*N*′-formyl-*gem*-diamine **4Zd** accompanied by symmetrical urea **5** in an approximate 70:30 ratio. It is interesting that the reduction of the carbamoyl azide function with $NaBH_4$ exclusively afforded *N*-formyl derivative **4Zd** and not *N*-methylamine **6** (see Scheme 2).



Scheme 2.

However, under our experimental conditions, $NaBH_4$ in the presence of a large amount of water increased the pH[29] and favored the hydrolysis of carbamoyl azide **1Zd** into the corresponding amine **7**, which in the presence of unreacted **1Zd** gave symmetrical urea **5** (see Scheme 3).[25]

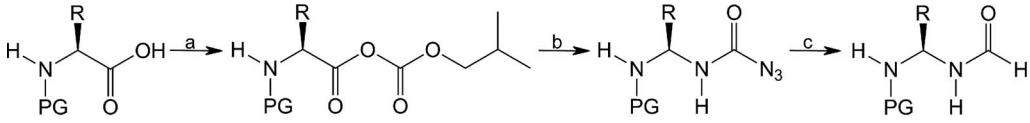


Scheme 3.

To reduce as much as possible the contact of $NaBH_4$ with water, the reaction was carried out as previously described, but, instead, it was gently stirred. As expected, the reaction was slower, and after 4 h, only 37% of **1Zd** was converted into *N*-formyl **4Zd**. The symmetrical urea **5** was absent. These preliminary results pointed out that the presence of water greatly affected the course of the reaction. In fact, when the reduction was performed on the separated organic phase (THF) that contained carbamoyl azide **1Zd** at room temperature, a lesser amount of $NaBH_4$ (2.5 equiv. with respect to **1Zd**) was used, and the ESI-MS analysis of the intact mixture showed that after 45 min, there was complete conversion of **1Zd** into the corresponding *N*-formyl derivative **4Zd**. On the basis of these experimental findings, the present protocol was successfully extended to other *N*-Boc/Fmoc/Z-protected α-amino acids **2** (see Table 1).

The obtained results as well as some properties of the *N*-protected *N*′-formyl-*gem*-diamines **4** prepared are reported in Table 2.

Table 1. Synthesis of formamides **4** derived from *N*-protected α-amino acids.[a]



2 **3** **1** **4**

1–4	PG[b]	R	1–4	PG[b]	R
Ba	Boc	CH_3	**Fe**	Fmoc	1*H*-indole-3-CH_2
Bb	Boc	$(CH_3)_2CH$	**Ff**	Fmoc	$CH_3S(CH_2)_2$
Bc	Boc	$(CH_3)_2CHCH_2$	**Za**	Cbz	CH_3
Bd	Boc	$PhCH_2$	**Zc**	Cbz	$(CH_3)_2CHCH_2$
Fa	Fmoc	CH_3	**Zd**	Cbz	$PhCH_2$
Fb	Fmoc	$(CH_3)_2CH$	**Ze**	Cbz	1*H*-indole-3-CH_2
Fc	Fmoc	$(CH_3)_2CHCH_2$	**Zg**	Cbz	$NH_2CO(CH_2)_2$
Fd	Fmoc	$PhCH_2$			

[a] Reagents and conditions: (a) *N*-methylmorpholine (NMM, 1.03 equiv.), THF, isobutyl chloroformate (IBCF, 1.10 equiv.), 10 min at –15 °C; (b) KH_2PO_4 (0.50 equiv.), H_2O and then KH_2PO_4 (5.00 equiv.), NaN_3 (2.50 equiv.), H_2O, 30 min at 0 °C and then 1.5 h at 45 °C; (c) separation of the organic phase (THF) and then $NaBH_4$ (2.50 equiv.), 45 min at room temp. [b] Boc = *tert*-butoxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl, Cbz = benzyloxycarbonyl.

Table 2. Yields and properties of formamides **4** derived from *N*-protected α-amino acids.

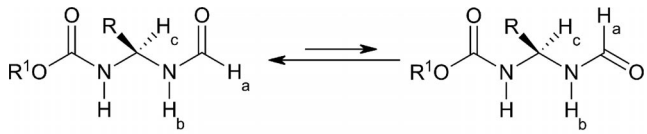
Product[a]	Solvent for recrystallization	% Yield[b]	M.p. [°C]	$[\alpha]_D^{20}$ (*c*, solvent)	*cis*/*trans*[c]
Boc-*g*Ala-CO-H (**4Ba**)	$CHCl_3$/hexane	83	118–120	+7.02 (*c* = 0.6, MeOH)	60:40
Boc-*g*Val-CO-H (**4Bb**)	toluene	84	182–184	+15.93 (*c* = 0.8, MeOH)	65:35
Boc-*g*Leu-CO-H (**4Bc**)	$CHCl_3$/hexane	86	126–128	+4.84 (*c* = 0.8, MeOH)	66:34
Boc-*g*Phe-CO-H (**4Bd**)	toluene	85	169–171	+22.60 (*c* = 0.9, MeOH)	67:33
Fmoc-*g*Ala-CO-H (**4Fa**)	toluene	81	212–214[d]	+38.81 (*c* = 0.3, MeOH)[d]	66:34
Fmoc-*g*Val-CO-H (**4Fb**)	$CHCl_3$/hexane	80	223–225[e]	+19.10 (*c* = 0.7, MeOH)[e]	66:34
Fmoc-*g*Leu-CO-H (**4Fc**)	$CHCl_3$/hexane	84	184–186[f]	+29.92 (*c* = 0.5, MeOH)[f]	73:27
Fmoc-*g*Phe-CO-H (**4Fd**)	toluene	89	225–227 (dec)	+5.54 (*c* = 0.9, DMSO)	68:32
Fmoc-*g*Trp-CO-H (**4Fe**)	toluene	94	238–240 (dec)	+3.40 (*c* = 0.6, DMSO)	68:32
Fmoc-*g*Met-CO-H (**4Ff**)	toluene	91	192–194[g]	+19.90 (*c* = 0.4, MeOH)[g]	66:34
Cbz-*g*Ala-CO-H (**4Za**)	toluene	85	143–145[h]	+14.84 (*c* = 0.3, DMSO)	60:40
Cbz-*g*Leu-CO-H (**4Zc**)	toluene	87	126–128[i]	+13.78 (*c* = 0.5, DMSO)	64:36
Cbz-*g*Phe-CO-H (**4Zd**)	$CHCl_3$/hexane	80	192–194[j]	+4.71 (*c* = 0.4, DMSO)	61:39
Cbz-*g*Trp-CO-H (**4Ze**)	toluene	93	181–183	+7.11 (*c* = 0.4, DMSO)	60:40
Cbz-*g*Gln-CO-H (**4Zg**)	AcOEt/MeOH	83	184–186	+5.69 (*c* = 0.5, DMSO)	60:40

[a] The *g* notation represents the *gem*-diamine derivative (see ref.[24n]). [b] Isolated yield. [c] Determined by ^1H NMR integration of the two distinct N–CH–N signals that are generated by the two rotamers (conformations of the two rotamers were defined as *trans* for rotamer A and *cis* for rotamer B). [d] Ref.[22b] m.p. 178 °C, $[\alpha]_D^{24}$ = +1.22 [*c* = 0.9, dimethyl sulfoxide (DMSO)]. [e] Ref.[22b] m.p. 183 °C, $[\alpha]_D^{24}$ = +1.00 (*c* = 1.0, DMSO). [f] Ref.[22b] m.p. 156 °C, $[\alpha]_D^{24}$ = –2.00 (*c* = 1.2, DMSO). [g] Ref.[22b] m.p. 165 °C, $[\alpha]_D^{24}$ = –1.62 (*c* = 1.3, DMSO). [h] Ref.[22a] m.p. 132–33 °C. [i] Ref.[22a] m.p. 123–24 °C. [j] Ref.[22a] m.p. 174–75 °C.

With the aid of ESI-MS analysis, we observed that the rate of the reduction (45 min) was not influenced by the nature of the α-*N*-protection and the amino acid side chain that was present in the starting carbamoyl azide **1**.

All the ^1H and ^{13}C NMR spectroscopic data of **4**, which were recorded in [D_6]DMSO, resulted in complex spectra, which was evidence of the presence of two rotameric forms in solution as a result of the restricted rotation around the N–CO formyl bond (see Table 3). (The conformations of the two rotamers were defined as *trans* for rotamer A and *cis* for rotamer B) In particular, the ^1H NMR spectra exhibited a broad doublet ($^3J_{bc}$ = 7.3–9.4 Hz) and a doublet of doublets ($^3J_{ab}$ = 1.6–1.8 Hz, $^4J_{ac}$ = 0.6–0.8 Hz) in the ranges from δ = 7.93 to 8.38 ppm and δ = 7.89 to 8.00 ppm, which were assigned to H_b and H_a, respectively, of the *N*-formyl moiety of the *cis* isomer (see Table 3, rotamer B). When the H_a and H_b resonances of the *trans* isomer did not overlap (see Table 3, rotamer A), they appeared as a doublet ($^3J_{ab}$ = 11.3–11.6 Hz) and a broad triplet (*J* = 10.1–10.3 Hz) in the δ range of 7.98–8.16 and 7.77–8.13 ppm, respectively. The assignments of the resonances were made on the basis of the assumption that the *trans* proton-proton coupling constant (i.e., $^3J_{ab}$) was greater than that of the *cis* isomer.[30] Moreover, the carbamate NH resonance, which was sometimes obscured by overlapping aromatic signals, appeared as a broad singlet in the δ range 7.18–7.93 and 6.92–7.70 ppm for the *trans* and *cis* isomer, respectively (see Table 3). Finally, the H_c proton, linked to the α-carbon of the starting amino acid, appeared as a multiplet (*J* = 7.0–8.1 Hz) in the range from δ = 5.02 to 5.56 ppm for rotamer B and from δ = 4.44 to 5.26 ppm for rotamer A (see Table 3). The ratio of the two isomers, as deduced from the integration of the two N–CH–N signals of **4**, ranged from 60:40 to 73:27 in favor of the *cis* isomer (see Table 2).

Table 3. ^{1}H NMR spectroscopic data of formamides **4** derived from *N*-protected α-amino acids.[a]



Product	δ NH$_b$COH_a [*J* in Hz]		δ NH_bCOH$_a$ [*J* in Hz]		δ NHCOO		δ N–CH$_c$–N [*J* in Hz]	
	cis	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
Boc-*g*Ala-CO-H	7.89, dd	8.12, d	8.04, br. d	7.82, br. t	7.06, br. s	7.26, br. s	5.29, sext	4.93, sext
(**4Ba**)	(1.6, 0.8)	(11.5)	(7.6)	(10.3)			(7.0)	(7.0)
Boc-*g*Val-CO-H	7.97, dd	8.06, d	7.93, br. d	7.77, br. t	6.92, br. s	7.18, br. s	5.02, q	4.44, q
(**4Bb**)	(1.8, 0.6)	(11.5)	(9.4)	(10.2)			(8.1)	(8.1)
Boc-*g*Leu-CO-H	7.92, dd	8.12, d	7.96, br. d	7.81, br. t	6.98, br. s	7.25, br. s	5.29, quint	4.79, quint
(**4Bc**)	(1.6, 0.6)	(11.5)	(9.1)	(10.3)			(7.7)	(7.9)
Boc-*g*Phe-CO-H	7.92, dd	overlapped	8.23, br. d	overlapped	overlapped	7.48, br. s	5.38, quint	4.96, quint
(**4Bd**)	(1.6, 0.6)		(7.6)				(7.7)	(7.8)
Fmoc-*g*Ala-CO-H	7.53, dd	overlapped	8.18, br. d	overlapped	7.65, br. s	7.84, br. s	5.38, sext	4.99, sext
(**4Fa**)	(1.6, 0.6)		(7.6)				(7.0)	(7.0)
Fmoc-*g*Val-CO-H	7.99, dd	overlapped	overlapped	overlapped	7.59, br. s	overlapped	5.08, q	4.50, q
(**4Fb**)	(1.6, 0.6)						(8.1)	(8.1)
Fmoc-*g*Leu-CO-H	7.95, dd	overlapped	overlapped	overlapped	overlapped	overlapped	5.37, quint	4.86, quint
(**4Fc**)	(1.6, 0.6)						(7.6)	(7.6)
Fmoc-*g*Phe-CO-H	7.96, dd	overlapped	8.32, br. d	overlapped	overlapped	overlapped	5.46, quint	5.05, quint
(**4Fd**)	(1.6, 0.6)		(7.6)				(7.6)	(7.6)
Fmoc-*g*Trp-CO-H	8.00, dd	overlapped	8.30, br. d	overlapped	overlapped	overlapped	5.41–5.73, m	4.95–5.24, m
(**4Fe**)	(1.6, 0.6)		(7.6)					
Fmoc-*g*Met-CO-H	7.98, dd	overlapped	8.21, br. d	overlapped	7.59, br. s	7.79, br. s	5.38, quint	4.96, quint
(**4Ff**)	(1.6, 0.6)		(8.0)				(7.3)	(7.3)
Cbz-*g*Ala-CO-H	7.91, dd	8.15, d	8.23, br. d	7.99, br. t	7.66, br. s	7.85, br. s	5.37, sext	4.91–5.12, m
(**4Za**)	(1.6, 0.8)	(11.6)	(7.3)	(10.1)			(7.0)	
Cbz-*g*Leu-CO-H	7.94, dd	8.16, d	8.22, br. d	7.99, br. t	7.60, br. s	7.83, br. s	5.38, quint	4.77–4.96, m
(**4Zc**)	(1.7, 0.8)	(11.6)	(7.4)	(10.2)			(7.6)	
Cbz-*g*Phe-CO-H	7.94, dd	7.98, d	8.38, br. d	8.13, br. t	7.54, br. s	7.78, br. s	5.46, quint	5.02–5.19, m
(**4Zd**)	(1.8, 0.8)	(11.3)	(7.8)	(10.1)			(7.5)	
Cbz-*g*Trp-CO-H	7.98, dd	overlapped	8.35, br. d	overlapped	7.70, br. s	7.93, br. s	5.56, quint	5.05–5.26, m
(**4Ze**)	(1.6, 0.8)		(7.6)				(7.5)	
Cbz-*g*Gln-CO-H	7.95, dd	overlapped	8.24, br. d	overlapped	7.65, br. s	7.85, br. s	5.27, quint	4.85, quint
(**4Zg**)	(1.6, 0.6)		(7.3)				(7.6)	(7.6)

[a] [D$_6$]DMSO as solvent, δ values in ppm.

To support our assignments, we carried out two ^{1}H-^{1}H decoupling experiments on Boc-*g*Ala-CO-H (**4Ba**) by irradiating the two apparent sextets (J = 7.0 Hz) that are generated by the N–CH–N proton of rotamer A and B and are centered at δ = 4.93 and 5.29 ppm, respectively (see Table 3). The irradiation of the higher field multiplet (*trans* isomer) collapsed the broad N–H formyl triplet (δ = 7.82 ppm, J = 10.3 Hz) into a broad doublet centered at the same chemical shift (δ = 7.82 ppm) and with a coupling constant (J = 11.5 Hz) that is identical to that observed for the corresponding formyl proton (doublet at δ = 8.12 ppm, $^3J_{ab}$ = 11.5 Hz, see Table 3). On the other hand, irradiation of the lower field multiplet (*cis* isomer) caused the broad N–H formyl doublet (δ = 8.04 ppm, J = 7.6 Hz) to become a broad singlet at the same frequency (see Table 3). Moreover, the doublet of doublets (δ = 7.89 ppm, $^3J_{ab}$ = 1.6 Hz, $^4J_{ac}$ = 0.8 Hz), which was generated by the corresponding formyl proton, collapsed to a doublet at the same chemical shift and with a coupling constant identical to the $^3J_{ab}$ that was observed for the doublet of doublets (see Table 3). Upon treatment with D_2O, all the broad N–H signals disappeared from the ^{1}H NMR spectrum of Boc-*g*Ala-CO-H (**4Ba**). The two apparent sextets (δ = 4.93 and 5.29 ppm, J = 7.0 Hz), arising from the H$_c$ proton of rotamer A and B (Table 3), appeared as two quartets (J = 6.5 Hz) that were centered at δ = 4.93 and 5.29 ppm, respectively. The absence of the NH$_b$ proton also simplified the pattern of the formyl proton. The doublet of doublets of the *cis* isomer became a doublet centered at δ = 7.84 ppm with a coupling constant $^4J_{ac}$ = 0.6 Hz, and the doublet of the *trans* isomer collapsed into a singlet at δ = 8.04 ppm.

The ^{13}C NMR spectra of **4** showed that larger differences in the chemical shifts between the two isomers came from the N–CH–N and the formyl C=O carbons, with the *trans* isomer signals shifted downfield. In particular, the resonances of the N–CH–N carbons were in the range of δ = 52.4–60.7 ppm for the *cis* isomer and δ = 56.1–65.6 ppm for the *trans* isomer. The formyl C=O carbon signals ranged from δ = 159.7 to 160.3 ppm for the *cis* isomer and from δ = 163.9 to 164.9 ppm for the *trans* isomer.

To test the generality of the present protocol, we extended the reaction to some *N*-protected dipeptide acids **8**

(see Table 4). The critical steps in the overall reaction were the synthesis of mixed anhydride **9** and its reaction with NaN_3 through a Curtius rearrangement of the corresponding acyl azide to lead to carbamoyl azide **10**.[25] In fact, as previously reported,[31] the ESI-MS analysis of the intact mixture that was obtained after the synthesis of mixed anhydride **9** showed the complete conversion of **9** into the corresponding 2,4-disubstituted-5(4*H*)-oxazolone **11**, which was prone to racemization under basic conditions[32] (see Table 4).

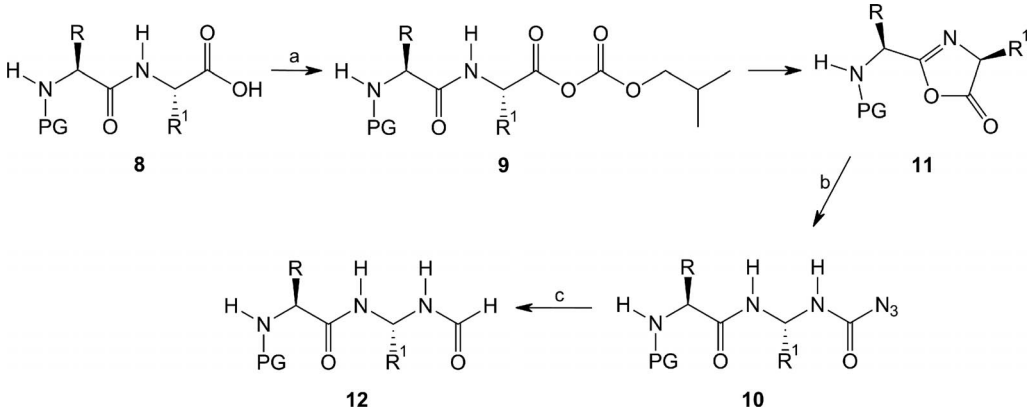
Under our experimental conditions, the reaction of NaN_3 with **11** occurred in the presence of aqueous KH_2PO_4, which maintained the mixture at pH ≈ 7. Moreover, with respect to the protocol for the syntheses of the *N*-protected *N*′-formyl-*gem*-diamines **4**, the reaction time for the preparation of mixed anhydride **9** was reduced from 10 to 5 min in this case, and the subsequent reaction of oxazolone **11** with NaN_3 was initially carried out at a lower temperature (–15 °C).

To exclude any incursion of racemization under our experimental conditions, Fmoc-L-Leu-L-*g*Phg-CO-H (**12Fch**) was prepared starting from Fmoc-L-Leu-L-Phg-OH (**8Fch**). The HPLC-ESI-MS profile of the intact reaction mixture was compared with that of the diastereoisomeric derivative Fmoc-L-Leu-DL-*g*Phg-CO-H (diast-**12Fch**) obtained employing a 50:50 diastereoisomeric mixture of Fmoc-L-Leu-DL-Phg-OH (diast-**8Fch**). The HPLC-ESI-MS analysis of diast-**12Fch** showed two distinct peaks with retention times (R_t) = 58.3 and 58.8 min with the same area, whereas that obtained from **12Fch** exhibited only one peak at R_t = 58.8 min. The analogous chromatographic behavior was found for all the crude reaction mixtures that were obtained from the syntheses of *N*-protected *N*′-formyl-*gem*-diaminoalkyl derivatives **12** and confirmed that the present protocol proceeds with the retention of configuration. The results and some properties of *N*-protected dipeptidyl-*N*′-formamides **12** are reported in Table 5.

Also in this case, the complexity of the ^1H and ^{13}C NMR spectra of **12** was evidence of the presence of the two rotamers A (*trans* isomer) and B (*cis* isomer), which resulted from the restricted rotation around the N–CO formyl bond in the [D_6]DMSO solution. Similar to the ^1H NMR spectra of *gem*-diamines **4**, when the formyl proton of the *trans* isomer (rotamer A) did not overlap with another resonance, it appeared as a doublet (J = 11.2–11.5 Hz) that was centered from δ = 8.16 to 8.27 ppm, whereas that of the *cis* isomer (rotamer B) became a doublet (J = 1.2–1.4 Hz) in the range from δ = 7.91 to 8.10 ppm. These two doublets collapsed into two singlets upon treatment with D_2O. The integration of the two distinct N–CH–N signals, which were generated by the two rotamers, showed that the *cis* isomer was also the more abundant isomer of the *N*-protected *N*′-formyl-*gem*-diaminoalkyl derivatives **12** (see Table 5, 65–78%).

Despite the presence of the two isomers, all the ^{13}C NMR spectra of **12** exhibited a single set of peaks for the carbons of the carbamate moiety. Otherwise, as expected, larger differences in the chemical shifts were observed for the N–CH–N and C=O carbon signals. In particular, the resonance of the N–CH–N carbon was in the range of δ = 50.8–55.7 ppm and 54.2–60.1 ppm for the *cis* and *trans* isomer, respectively. The formyl and the amide C=O carbons of the *cis* isomer (rotamer B) appeared in the range of δ =

Table 4. Synthesis of formamides **12** derived from *N*-protected dipeptide acids.[a]



8–**12**	PG	R	R^1
Bbe	Boc	$(CH_3)_2CH$	1*H*-indole-3-CH_2
Bcd	Boc	$(CH_3)_2CHCH_2$	$PhCH_2$
Fca	Fmoc	$(CH_3)_2CHCH_2$	CH_3
Fch	Fmoc	$(CH_3)_2CHCH_2$	Ph
Fda	Fmoc	$PhCH_2$	CH_3
Zda	Cbz	$PhCH_2$	CH_3
Zdd	Cbz	$PhCH_2$	$PhCH_2$

[a] Reagents and conditions: (a) NMM (1.03 equiv.), THF, IBCF (1.10 equiv.), 5 min at –15 °C; (b) KH_2PO_4 (0.50 equiv.), H_2O and then KH_2PO_4 (5.00 equiv.), NaN_3 (2.50 equiv.), H_2O, 15 min at –15 °C, then 15 min at 0 °C, and then 1.5 h at 45 °C; (c) separation of the organic phase (THF) and then $NaBH_4$ (2.50 equiv.), 45 min at room temp.

Table 5. Yields and properties of formamides **12** derived from *N*-protected dipeptide acids.

Product	Solvent for recrystallization	% Yield[a]	M.p. [°C]	$[\alpha]_D^{20}$ (*c*, solvent)	*cis*/*trans*[b]
Boc-Val-*g*Trp-CO-H (**12Bbe**)	$CHCl_3$/hexane	82	170–172	–4.87 (*c* = 0.6, DMSO)	67:33
Boc-Leu-*g*Phe-CO-H (**12Bcd**)	toluene	80	173–175	–8.81 (*c* = 0.2, DMSO)	65:35
Fmoc-Leu-*g*Ala-CO-H (**12Fca**)	$CHCl_3$/hexane	80	214–216	+4.1 (*c* = 0.5, DMSO)	62:38
Fmoc-Leu-*g*Phg-CO-H (**12Fch**)	$CHCl_3$/hexane	81	223–225	–3.75 (*c* = 0.3, DMSO)	78:22
Fmoc-Phe-*g*Ala-CO-H (**12Fda**)	toluene/EtOAc	72	230–232	+15.87 (*c* = 0.1, DMSO)	65:35
Cbz-Phe-*g*Ala-CO-H (**12Zda**)	toluene	77	211–213[c]	+26.67 (*c* = 0.4, DMSO)	65:35
Cbz-Phe-*g*Phe-CO-H (**12Zdd**)	toluene	87	232–234	+8.48 (*c* = 0.9, DMSO)	67:33

[a] Isolated yield. [b] Determined by ^{1}H NMR integration of the two distinct N–CH–N signals that are generated by the two rotamers. (Conformations of the two rotamers were defined to be *trans* for rotamer A and *cis* for rotamer B). [c] Ref.[22a] m.p. 158–60 °C.

159.9–160.4 ppm and 170.4–171.7 ppm, whereas for the *trans* isomer (rotamer A), these signals shifted downfield to a range from δ = 163.9 to 164.5 ppm and from δ = 171.0 to 172.3 ppm, respectively.

Conclusions

In summary, we have developed a synthetic method for the preparation of *N*-protected *N*′-formyl-*gem*-diaminoalkyl derivatives **4** and **12** through the unprecedented reduction of the carbamoyl azide of *N*-protected α-amino acids and dipeptides with $NaBH_4$. In contrast to other reported methods, this simple, efficient, and racemization-free protocol is compatible with the most commonly used *N*-protecting groups (Boc, Fmoc, Cbz). The complexity exhibited by ^{1}H and ^{13}C NMR spectra of the *N*-protected *N*′-formyl-*gem*-diaminoalkyl derivatives **4** and **12** highlighted the presence of two rotamers in the [D_6]DMSO solution, with the *cis* isomer predominating. These compounds may be useful building blocks in the syntheses of biologically active compounds that contain an asymmetric *gem*-diamine moiety, such as partially modified retro-inverso peptides.

Experimental Section

General Methods: *N*-protected dipeptide acids **8** were prepared by a reported procedure.[31] All solvents and reagents were purchased from Aldrich Chemical Company and used without further purification. The reactions were monitored by ESI-MS in the positive and negative ion modes with a Finnigan LXQ (linear trap) by diluting the intact reaction mixture with methanol and directly infusing the resulting solution into the ion source with the aid of a syringe pump. HPLC-ESI-MS analyses were performed with the same instrument coupled to a Dionex UltiMate 3000 RS Pump and equipped with a Dionex UltiMate 3000 RS Autosampler. The LC separations were performed with a Hypersil AA-ODS column (200 mm × 2.1 mm, 5 mm) from Agilent Technologies that operated at 30 °C with a flow rate of 0.2 mL/min and a mobile phase composed of water (A) and methanol (B). The proportion of solvent B was linearly increased to 80% over a period of 50 min and kept at this concentration until the end of the run. IR spectra were obtained by the KBr technique for solids with a Bruker Vector 22 spectrophotometer and recorded in the range of 4000–400 cm^{-1}. The ^{1}H and ^{13}C NMR spectroscopic data were recorded in [D_6]-DMSO at 40 °C with a Bruker AC-F 200 spectrometer at 200 and 50 MHz, respectively. The NMR resonances are reported as δ values relative to TMS (0 ppm). Some ^{1}H NMR multiplets are characterized by the term app (apparent), and this refers only to the appearance and may be an oversimplification. To assign the resonances of the N–CH–NH–CO–H protons of the two isomers (rotamers A and B), ^{1}H-^{1}H decoupling experiments were performed by irradiating the corresponding N–CH–N proton at the center of its signal. Optical rotations were measured in suitable solutions (g/100 mL) at 20 °C with an AP-300 automatic polarimeter from ATAGO. Elemental analyses were performed with a FlashEA 1112 Series CHNS-O elemental analyser. Melting points were determined with an automatic Mettler (Mod. FP61) melting point apparatus.

General Procedure for the Synthesis of Formamides 4 Derived from *N*-Protected α-Amino Acids: *N*-methylmorpholine (0.28 mL, 2.58 mmol) was slowly added to a stirred solution of *N*-protected α-amino acid **2** (2.50 mmol) in THF (20 mL). After 5 min, isobutyl chloroformate (0.36 mL, 2.75 mmol) was slowly added to the reaction mixture, which was cooled to –15 °C. The stirring was continued for 10 min at the same temperature. The reaction mixture was subsequently warmed to 0 °C, and an aqueous solution of KH_2PO_4 (1.4 M, 0.89 mL, 1.25 mmol) was added in one portion followed, after 5 min, by the addition of an aqueous solution of KH_2PO_4 (1.4 M, 8.93 mL, 12.50 mmol) and NaN_3 (0.41 g, 6.25 mmol). After 30 min at 0 °C, the mixture was warmed to 45 °C, stirred for 1.5 h, and then cooled to room temperature. The organic phase was separated. Powdered $NaBH_4$ (0.24 g, 6.25 mmol) was rapidly added to the THF solution of carbamoyl azide **1** at room temperature with vigorous stirring. After an additional 45 min, the THF was removed under reduced pressure. The crude residue was dissolved in AcOEt (80 mL), and the resulting solution was washed sequentially with 5% HCl (10 mL), water (10 mL), 5% Na_2CO_3 (10 mL), water (10 mL), and then a saturated brine solution (10 mL). The organic layer was finally dried with Na_2SO_4. After filtration and evaporation in vacuo of the solvent, the crude product was recrystallized from suitable solvents to afford the *N*-protected *N*′-formyl-*gem*-diaminoalkyl derivatives **4** in 80–94% overall yield (see Table 2).

Boc-*g*Ala-CO-H (4Ba): IR (KBr): $\tilde{\nu}$ = 3249, 2984, 1716, 1682, 1647, 1532, 1397, 1367, 1324, 1245, 1157, 1140, 1111, 1052, 760, 615 cm^{-1}. MS (ESI+): *m*/*z* = 211 $[M + Na]^+ \rightarrow (MS^2)$ 155, 111. $C_8H_{16}N_2O_3$ (188.23): calcd. C 51.05, H 8.57, N 14.88; found C 51.10, H 8.55, N 14.85. Data for *trans* isomer: ^{1}H NMR: δ = 1.24 (app t, *J* = 6.5 Hz, 3 H, CH_3), 1.38 [s, 9 H, $(CH_3)_3C$], 4.93 (app sext, *J* = 7.0 Hz, 1 H, *g*CH), 7.26 (br. s, 1 H, NHCOO), 7.82 (br. t, *J* = 10.3 Hz, 1 H, N*H*COH), 8.12 (d, *J* = 11.5 Hz, 1 H, HCO) ppm. ^{13}C NMR: δ = 20.6, 28.0, 56.1, 78.1, 154.4, 163.9 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 1.24 (app t, *J* = 6.5 Hz, 3 H, CH_3), 1.38 [s, 9 H, $(CH_3)_3C$], 5.29 (app sext, *J* = 7.0 Hz, 1 H, *g*CH), 7.06 (br. s, 1 H, NHCOO), 7.89 (dd, *J* = 1.6, 0.8 Hz, 1 H, HCO), 8.04 (br. d, *J* = 7.6 Hz, 1 H, N*H*COH) ppm. ^{13}C NMR: δ = 20.8, 28.0, 52.4, 77.9, 154.0, 159.7 ppm.

Boc-*g*Val-CO-H (4Bb): IR (KBr): $\tilde{\nu}$ = 3312, 2984, 2970, 2870, 1688, 1670, 1544, 1501, 1380, 1363, 1345, 1295, 1245, 1212, 1172, 1148, 1121, 1044, 1007, 711, 651 cm^{-1}. MS (ESI+): *m*/*z* = 239 [M + Na]$^+ \rightarrow$(MS^2) 183, 139. $C_{10}H_{20}N_2O_3$ (216.28): calcd. C 55.53, H 9.32, N 12.95; found C 55.55, H 9.30, N 12.99. Data for *trans* isomer: ^{1}H NMR: δ = 0.86 and 0.89 [2 d, *J* = 6.2, 6.2 Hz, 6 H, (C*H*$_3$)$_2$CH], 1.39 [s, 9 H, (CH$_3$)$_3$C], 1.68–1.95 [m, 1 H, (CH$_3$)$_2$C*H*], 4.44 (app q, *J* = 8.1 Hz, 1 H, *g*CH), 7.18 (br. s, 1 H, NHCOO), 7.77 (br. t, *J* = 10.5 Hz, 1 H, N*H*COH), 8.06 (d, *J* = 11.5 Hz, 1 H, HCO) ppm. ^{13}C NMR: δ = 18.4, 18.7, 20.1, 31.0, 65.6, 78.1, 154.8, 164.3 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 0.84 and 0.85 [2 d, *J* = 6.8, 6.8 Hz, 6 H, (C*H*$_3$)$_2$CH], 1.38 [s, 9 H, (CH$_3$)$_3$C], 1.68–1.95 [m, 1 H, (CH$_3$)$_2$C*H*], 5.02 (app q, *J* = 8.1 Hz, 1 H, *g*CH), 6.92 (br. s, 1 H, NHCOO), 7.93 (br. d, *J* = 9.4 Hz, 1 H, N*H*COH), 7.97 (dd, *J* = 1.8, 0.6 Hz, 1 H, HCO) ppm. ^{13}C NMR: δ = 17.9, 18.0, 20.1, 31.7, 60.6, 77.8, 154.5, 160.1 ppm.

Boc-*g*Leu-CO-H (4Bc): IR (KBr): $\tilde{\nu}$ = 3335, 3320, 2957, 1688, 1652, 1545, 1502, 1394, 1367, 1290, 1234, 1213, 1157, 1144, 1061, 708, 636 cm^{-1}. MS (ESI+): *m*/*z* = 253 [M + Na]$^+ \rightarrow$(MS^2) 197, 153. $C_{11}H_{22}N_2O_3$ (230.31): calcd. C 57.37, H 9.63, N 12.16; found C 57.40, H 9.65, N 12.15. Data for *trans* isomer: ^{1}H NMR: δ = 0.86 [d, *J* = 6.5 Hz, 6 H, (C*H*$_3$)$_2$CH], 1.39 [s, 9 H, (CH$_3$)$_3$C], 1.38–1.70 (m, 3 H, CHCH$_2$), 4.79 (app quint, *J* = 7.9 Hz, 1 H, *g*CH), 7.25 (br. s, 1 H, NHCOO), 7.81 (br. t, *J* = 10.3 Hz, 1 H, N*H*COH), 8.12 (d, *J* = 11.5 Hz, 1 H, HCO) ppm. ^{13}C NMR: δ = 21.6, 22.0, 23.8, 28.0, 42.2, 58.4, 78.1, 154.1, 164.0 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 0.87 [d, *J* = 6.2 Hz, 6 H, (C*H*$_3$)$_2$CH], 1.38 [s, 9 H, (CH$_3$)$_3$C], 1.38–1.70 (m, 3 H, CHCH$_2$), 5.29 (app quint, *J* = 7.7 Hz, 1 H, *g*CH), 6.98 (br. s, 1 H, NHCOO), 7.92 (dd, *J* = 1.6, 0.6 Hz, 1 H, HCO), 7.96 (br. d, *J* = 9.1 Hz, 1 H, N*H*COH) ppm. ^{13}C NMR: δ = 21.9, 22.1, 24.0, 28.0, 43.3, 54.2, 77.8, 154.2, 159.8 ppm.

Boc-*g*Phe-CO-H (4Bd): IR (KBr): $\tilde{\nu}$ = 3350, 3323, 2989, 1690, 1664, 1540, 1496, 1391, 1366, 1297, 1220, 1171, 1009, 699 cm^{-1}. MS (ESI+): *m*/*z* = 287 [M + Na]$^+ \rightarrow$(MS^2) 231, 187. $C_{14}H_{20}N_2O_3$ (264.32): calcd. C 63.62, H 7.63, N 10.60; found C 63.61, H 7.65, N 10.57. Data for *trans* isomer: ^{1}H NMR: δ = 1.37 [s, 9 H, (CH$_3$)$_3$C], 2.76–3.02 (m, 2 H, CH$_2$), 4.96 (app quint, *J* = 7.8 Hz, 1 H, *g*CH), 7.12–7.35 (m, 5 H, Ar), 7.48 (br. s, 1 H, NHCOO), 7.93–8.02 (m, 2 H, NHCOH) ppm. ^{13}C NMR: δ = 28.0, 39.7, 61.4, 78.3, 126.2, 128.0, 129.3, 137.1, 154.2, 164.0 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 1.34 [s, 9 H, (CH$_3$)$_3$C], 2.76–3.02 (m, 2 H, CH$_2$), 5.38 (app quint, *J* = 7.7 Hz, 1 H, *g*CH), 7.12–7.35 (m, 6 H, Ar, NHCOO), 7.92 (dd, *J* = 1.6, 0.6 Hz, 1 H, HCO), 8.23 (br. d, *J* = 7.6 Hz, 1 H, N*H*COH) ppm. ^{13}C NMR: δ = 28.0, 40.1, 57.2, 78.0, 126.1, 127.9, 129.1, 137.3, 154.5, 160.0 ppm.

Fmoc-*g*Ala-CO-H (4Fa): IR (KBr): $\tilde{\nu}$ = 3296, 1696, 1655, 1544, 1504, 1445, 1385, 1343, 1264, 1222, 1203, 1105, 1083, 1058, 736 cm^{-1}. MS (ESI+): *m*/*z* = 333 [M + Na]$^+ \rightarrow$(MS^2) 288. $C_{18}H_{18}N_2O_3$ (310.35): calcd. C 69.66, H 5.85, N 9.03; found C 69.63, H 5.88, N 9.00. Data for *trans* isomer: ^{1}H NMR: δ = 1.30 (d, *J* = 6.5 Hz, 3 H, CH$_3$), 4.15–4.40 (m, 3 H, CHCH$_2$O), 4.99 (app sext, *J* = 7.0 Hz, 1 H, *g*CH), 7.27–7.48 (m, 4 H, Ar), 7.66–7.75 (m, 2 H, Ar), 7.84 (br. s, 1 H, NHCOO), 7.85–7.91 (m, 2 H, Ar), 7.95–8.10 (m, 2 H, NHCOH) ppm. ^{13}C NMR: δ = 20.5, 46.6, 56.4, 65.4, 119.9, 124.9, 126.9, 127.4, 140.6, 143.7, 155.0, 163.9 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 1.28 (d, *J* = 6.5 Hz, 3 H, CH$_3$), 4.15–4.40 (m, 3 H, CHCH$_2$O), 5.38 (app sext, *J* = 7.0 Hz, 1 H, *g*CH), 7.27–7.48 (m, 4 H, Ar), 7.65 (br. s, 1 H, NHCOO), 7.66–7.75 (m, 2 H, Ar), 7.85–7.91 (m, 2 H, Ar), 7.93 (dd, *J* = 1.6, 0.6 Hz, 1 H, HCO), 8.18 (br. d, *J* = 7.6 Hz, 1 H, N*H*COH) ppm. ^{13}C NMR: δ = 20.7, 46.6, 52.7, 65.3, 119.9, 125.0, 126.9, 127.4, 140.6, 143.6, 154.6, 159.8 ppm.

Fmoc-*g*Val-CO-H (4Fb): IR (KBr): $\tilde{\nu}$ = 3299, 2974, 2961, 1692, 1661, 1646, 1551, 1511, 1464, 1451, 1385, 1339, 1294, 1250, 1207, 1018, 735 cm^{-1}. MS (ESI+): *m*/*z* = 361 [M + Na]$^+ \rightarrow$(MS^2) 316. $C_{20}H_{22}N_2O_3$ (338.41): calcd. C 70.99, H 6.55, N 8.28; found C 71.02, H 6.52, N 8.25. Data for *trans* isomer: ^{1}H NMR: δ = 0.90 and 0.91 [2 d, *J* = 6.1, 6.1 Hz, 6 H, (C*H*$_3$)$_2$CH], 1.72–1.99 [m, 1 H, (CH$_3$)$_2$C*H*], 4.15–4.38 (m, 3 H, CHCH$_2$O), 4.50 (app q, *J* = 8.1 Hz, 1 H, *g*CH), 7.25–7.48 (m, 4 H, Ar), 7.65–7.77 (m, 2 H, Ar), 7.79–7.96 (m, 4 H, Ar, N*H*COH, NHCOO), 8.02–8.14 (m, 1 H, HCO) ppm. ^{13}C NMR: δ = 18.6, 18.8, 31.0, 46.6, 66.0, 65.5, 120.0, 125.0, 127.0, 127.5, 140.6, 143.8, 155.6, 164.4 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 0.85 and 0.86 [2 d, *J* = 6.7, 6.7 Hz, 6 H, (C*H*$_3$)$_2$CH], 1.72–1.99 [m, 1 H, (CH$_3$)$_2$C*H*], 4.15–4.38 (m, 3 H, CHCH$_2$O), 5.08 (app q, *J* = 8.1 Hz, 1 H, *g*CH), 7.25–7.48 (m, 4 H, Ar), 7.59 (br. s, 1 H, NHCOO), 7.65–7.77 (m, 2 H, Ar), 7.79–7.96 (m, 2 H, Ar), 7.99 (dd, *J* = 1.6, 0.6 Hz, 1 H, HCO), 8.02–8.14 (m, 1 H, N*H*COH) ppm. ^{13}C NMR: δ = 18.0, 18.1, 31.7, 46.6, 60.7, 65.4, 120.0, 125.1, 127.0, 127.5, 140.6, 143.7, 155.1, 160.3 ppm.

Fmoc-*g*Leu-CO-H (4Fc): IR (KBr): $\tilde{\nu}$ = 3300, 2958, 2870, 1690, 1660, 1549, 1508, 1464, 1449, 1386, 1284, 1266, 1228, 1207, 735 cm^{-1}. MS (ESI+): *m*/*z* = 375 [M + Na]$^+ \rightarrow$(MS^2) 330. $C_{21}H_{24}N_2O_3$ (352.43): calcd. C 71.57, H 6.86, N 7.95; found C 71.60, H 6.81, N 7.97. Data for *trans* isomer: ^{1}H NMR: δ = 0.87 [d, *J* = 5.9 Hz, 6 H, (C*H*$_3$)$_2$CH], 1.35–1.69 (m, 3 H, CHCH$_2$), 4.15–4.41 (m, 3 H, CHCH$_2$O), 4.86 (app quint, *J* = 7.6 Hz, 1 H, *g*CH), 7.25–7.48 (m, 4 H, Ar), 7.63–7.77 (m, 2 H, Ar), 7.83–7.93 (m, 3 H, Ar, NHCOO), 8.01–8.24 (m, 2 H, HCO, N*H*COH) ppm. ^{13}C NMR: δ = 21.8, 22.0, 23.9, 42.1, 46.7, 58.7, 65.4, 120.0, 125.0, 127.0, 127.6, 140.7, 143.8, 155.5, 164.3 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 0.87 [d, *J* = 5.9 Hz, 6 H, (C*H*$_3$)$_2$CH], 1.35–1.69 (m, 3 H, CHCH$_2$), 4.15–4.41 (m, 3 H, CHCH$_2$O), 5.37 (app quint, *J* = 7.6 Hz, 1 H, *g*CH), 7.25–7.48 (m, 4 H, Ar), 7.63–7.77 (m, 3 H, Ar, NHCOO), 7.83–7.93 (m, 2 H, Ar), 7.95 (dd, *J* = 1.6, 0.6 Hz, 1 H, HCO), 8.01–8.24 (m, 1 H, N*H*COH) ppm. ^{13}C NMR: δ = 21.9, 22.2, 24.1, 43.2, 46.7, 54.4, 65.3, 120.0, 125.1, 127.0, 127.6, 140.7, 143.7, 154.9, 160.0 ppm.

Fmoc-*g*Phe-CO-H (4Fd): IR (KBr): $\tilde{\nu}$ = 3292, 3020, 1687, 1649, 1552, 1509, 1465, 1451, 1439, 1396, 1349, 1295, 1265, 1229, 1050, 1027, 735, 705 cm^{-1}. MS (ESI+): *m*/*z* = 409 [M + Na]$^+ \rightarrow$(MS^2) 364. $C_{24}H_{22}N_2O_3$ (386.45): calcd. C 74.59, H 5.74, N 7.25; found C 74.56, H 5.78, N 7.27. Data for *trans* isomer: ^{1}H NMR: δ = 2.80–3.08 (m, 2 H, Ph-CH$_2$), 4.12–4.40 (m, 3 H, CHCH$_2$O), 5.05 (app quint, *J* = 7.6 Hz, 1 H, *g*CH), 7.15–7.49 (m, 9 H, Ar), 7.59–7.75 (m, 2 H, Ar), 7.81–7.93 (m, 3 H, Ar, NHCOO), 7.99–8.17 (m, 2 H, NHCOH) ppm. ^{13}C NMR: δ = 39.7, 46.5, 61.7, 64.4, 119.9, 124.9, 126.3, 126.9, 127.5, 128.1, 129.2, 137.0, 140.6, 143.6, 155.2, 164.9 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 2.80–3.08 (m, 2 H, Ph-CH$_2$), 4.12–4.40 (m, 3 H, CHCH$_2$O), 5.46 (app quint, *J* = 7.6 Hz, 1 H, *g*CH), 7.15–7.49 (m, 9 H, Ar), 7.59–7.75 (m, 3 H, Ar, NHCOO), 7.81–7.93 (m, 2 H, Ar), 7.96 (dd, *J* = 1.6, 0.6 Hz, 1 H, HCO), 8.32 (br. d, *J* = 7.6 Hz, 1 H, N*H*COH) ppm. ^{13}C NMR: δ = 40.0, 46.5, 57.6, 65.4, 119.9, 125.0, 126.2, 126.9, 127.5, 128.0, 129.0, 137.2, 140.6, 143.7, 154.8, 160.1 ppm.

Fmoc-Trp-CO-H (4Fe): IR (KBr): $\tilde{\nu}$ = 3292, 3020, 1687, 1649, 1552, 1509, 1465, 1451, 1439, 1396, 1349, 1295, 1265, 1229, 1050, 1027, 735, 705 cm^{-1}. MS (ESI+): *m*/*z* = 448 [M + Na]$^+ \rightarrow$(MS^2) 403. $C_{26}H_{23}N_3O_3$ (425.49): calcd. C 73.39, H 5.45, N 9.88; found C 73.35, H 5.50, N 9.90. Data for *trans* isomer: ^{1}H NMR: δ = 3.07 (app d, *J* = 7.0 Hz, 2 H, Ar-CH$_2$), 4.06–4.43 (m, 3 H, CHCH$_2$O), 4.95–5.24 (m, 1 H, *g*CH), 6.93–7.49 (m, 8 H, Ar), 7.55–7.76 (m, 4 H, Ar, NHCOO), 7.82–7.93 (m, 2 H, Ar), 8.04–8.16 (m, 2 H, NHCOH), 10.81 (br. s, 1 H, Ar-NH) ppm. ^{13}C NMR: δ = 30.1,

46.5, 61.0, 65.5, 109.4, 111.2, 118.0, 118.3, 119.9, 120.7, 123.9, 124.9, 126.9, 127.0, 127.4, 136.0, 140.6, 143.7, 155.2, 163.9 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 3.07 (app d, J = 7.0 Hz, 2 H, Ar-CH_2), 4.06–4.43 (m, 3 H, $CHCH_2O$), 5.41–5.73 (m, 1 H, *g*CH), 6.93–7.49 (m, 9 H, Ar, NHCOO), 7.55–7.76 (m, 3 H, Ar), 7.82–7.93 (m, 2 H, Ar), 8.00 (dd, J = 1.6, 0.6 Hz, 1 H, HCO), 8.30 (br. d, J = 7.6 Hz, 1 H, N*H*COH), 10.77 (br. s, 1 H, Ar-NH) ppm. ^{13}C NMR: δ = 30.3, 46.5, 57.1, 65.4, 109.7, 111.3, 118.1, 118.2, 119.9, 120.7, 123.4, 125.0, 126.9, 127.3, 127.4, 136.0 140.5, 143.6, 154.9, 160.2 ppm.

Fmoc-*g*Met-CO-H (4Ff): IR (KBr): $\tilde{\nu}$ = 3298, 1695, 1645, 1549, 1507, 1444, 1394, 1285, 1263, 1203, 1078, 1050, 736 cm^{-1}. MS (ESI+): m/z = 393 [M + Na]$^+$→(MS^2) 348. $C_{20}H_{22}N_2O_3S$ (370.47): calcd. C 64.84, H 5.99, N 7.56, S 8.65; found C 64.87, H 5.98, N 7.58, S 8.62. Data for *trans* isomer: ^{1}H NMR: δ = 1.80–1.98 (m, 2 H, *g*CHC*H*$_2$), 2.04 (s, 3 H, SCH_3), 2.44 (app t, J = 7.6 Hz, 2 H, SCH_2), 4.16–4.44 (m, 3 H, $CHCH_2O$), 4.96 (app quint, J = 7.3 Hz, 1 H, *g*CH), 7.25–7.48 (m, 4 H, Ar), 7.64–7.76 (m, 2 H, Ar), 7.79 (br. s, 1 H, NHCOO), 7.83–7.92 (m, 2 H, Ar), 8.00–8.14 (m, 2 H, NHCOH) ppm. ^{13}C NMR: δ = 14.4, 29.1, 32.9, 46.6, 59.2, 65.4, 119.9, 124.9, 126.9, 127.5, 140.6, 143.7, 155.3, 164.2 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 1.80–1.98 (m, 2 H, *g*CHC*H*$_2$), 2.04 (s, 3 H, SCH_3), 2.44 (app t, J = 7.6 Hz, 2 H, SCH_2), 4.16–4.44 (m, 3 H, $CHCH_2O$), 5.38 (app quint, J = 7.3 Hz, 1 H, *g*CH), 7.25–7.48 (m, 4 H, Ar), 7.59 (br. s, 1 H, NHCOO), 7.64–7.76 (m, 2 H, Ar), 7.83–7.92 (m, 2 H, Ar), 7.98 (dd, J = 1.6, 0.6 Hz, 1 H, HCO), 8.21 (br. d, J = 8.0 Hz, 1 H, N*H*COH) ppm. ^{13}C NMR: δ = 14.5, 29.0, 33.7, 46.6, 55.4, 65.3, 119.9, 125.0, 126.9, 127.5, 140.6, 143.6, 154.9, 160.1 ppm.

Cbz-*g*Ala-CO-H (4Za): IR (KBr): $\tilde{\nu}$ = 3300, 2997, 1688, 1655, 1551, 1505, 1457, 1394, 1344, 1315, 1265, 1219, 1167, 1096, 1058, 721, 699 cm^{-1}. MS (ESI+): m/z = 245 [M + Na]$^+$→(MS^2) 200. $C_{11}H_{14}N_2O_3$ (222.24): calcd. C 59.45, H 6.35, N 12.60; found C 59.44, H 6.38, N 12.64. Data for *trans* isomer: ^{1}H NMR: δ = 1.29 (d, J = 6.5 Hz, 3 H, CH_3), 4.91–5.12 (m, 3 H, OCH_2, *g*CH), 7.24–7.44 (m, 5 H, Ar), 7.85 (br. s, 1 H, NHCOO), 7.99 (br. t, J = 10.1 Hz, 1 H, N*H*COH), 8.15 (d, J = 11.6 Hz, 1 H, HCO) ppm. ^{13}C NMR: δ = 20.6, 56.5, 65.3, 127.7, 127.8, 128.3, 136.8, 155.1, 164.1 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 1.26 (d, J = 6.7 Hz, 3 H, CH_3), 4.91–5.12 (m, 2 H, OCH_2), 5.37 (app sext, J = 7.0 Hz, 1 H, *g*CH), 7.24–7.44 (m, 5 H, Ar), 7.66 (br. s, 1 H, NHCOO), 7.91 (dd, J = 1.6, 0.8 Hz, 1 H, HCO), 8.23 (br. d, J = 7.3 Hz, 1 H, N*H*COH) ppm. ^{13}C NMR: δ = 20.8, 52.7, 65.2, 127.7, 127.8, 128.3, 136.9, 154.7, 159.9 ppm.

Cbz-*g*Leu-CO-H (4Zc): IR (KBr): $\tilde{\nu}$ = 3317, 3290, 2952, 1697, 1659, 1551, 1508, 1464, 1390, 1285, 1265, 1231, 1217, 1062, 1001, 743, 697 cm^{-1}. MS (ESI+): m/z = 287 [M + Na]$^+$→(MS^2) 242. $C_{14}H_{20}N_2O_3$ (264.32): calcd. C 63.62, H 7.63, N 10.60; found C 63.65, H 7.59, N 10.62. Data for *trans* isomer: ^{1}H NMR: δ = 0.85 [d, J = 6.2 Hz, 6 H, $(CH_3)_2CH$], 1.38–1.70 [m, 3 H, $CHCH_2$], 4.77–4.96 (m, 1 H, *g*CH), 5.04 (s, 2 H, OCH_2), 7.24–7.43 (m, 5 H, Ar), 7.83 (br. s, 1 H, NHCOO), 7.99 (br. t, J = 10.2 Hz, 1 H, N*H*COH), 8.16 (d, J = 11.6 Hz, 1 H, HCO) ppm. ^{13}C NMR: δ = 21.7, 22.0, 23.8, 42.1, 58.8, 65.4, 127.7, 127.8, 128.2, 136.8, 155.5, 164.2 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 0.86 [d, J = 6.2 Hz, 6 H, $(CH_3)_2CH$], 1.38–1.70 [m, 3 H, $CHCH_2$], 5.03 (s, 2 H, OCH_2), 5.38 (app quint, J = 7.6 Hz, 1 H, *g*CH), 7.24–7.43 (m, 5 H, Ar), 7.60 (br. s, 1 H, NHCOO), 7.94 (dd, J = 1.7, 0.8 Hz, 1 H, HCO), 8.22 (br. d, J = 7.4 Hz, 1 H, N*H*COH) ppm. ^{13}C NMR: δ = 21.9, 22.2, 24.0, 43.2, 54.5, 65.2, 127.7, 127.8, 128.2, 137.0, 154.9, 160.0 ppm.

Cbz-*g*Phe-CO-H (4Zd): IR (KBr): $\tilde{\nu}$ = 3318, 3290, 3062, 3033, 2930, 1693, 1655, 1544, 1509, 1455, 1392, 1349, 1288, 1264, 1225, 1187, 1047, 1014, 743, 696, 518 cm^{-1}. MS (ESI+): m/z = 321 [M + Na]$^+$→(MS^2) 276. $C_{17}H_{18}N_2O_3$ (298.34): calcd. C 68.44, H 6.08, N 9.39; found C 68.43, H 6.10, N 9.35. Data for *trans* isomer: ^{1}H NMR: δ = 2.79–3.05 (m, 2 H, *g*CHC*H*$_2$), 5.02 (s, 2 H, OCH_2), 5.02–5.19 (m, 1 H, *g*CH), 7.14–7.43 (m, 10 H, Ar), 7.78 (br. s, 1 H, NHCOO), 7.98 (d, J = 11.3 Hz, 1 H, HCO), 8.13 (br. t, J = 10.1 Hz, 1 H, N*H*COH) ppm. ^{13}C NMR: δ = 39.7, 61.8, 65.4, 126.4, 127.5, 127.8, 128.2, 128.3, 129.3, 136.7, 137.8, 155.2, 164.1 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 2.79–3.05 (m, 2 H, *g*CHC*H*$_2$), 5.00 (s, 2 H, OCH_2), 5.46 (app quint, J = 7.5 Hz, 1 H, *g*CH), 7.14–7.43 (m, 10 H, Ar), 7.54 (br. s, 1 H, NHCOO), 7.94 (dd, J = 1.8, 0.8 Hz, 1 H, HCO), 8.38 (br. d, J = 7.8 Hz, 1 H, N*H*COH) ppm. ^{13}C NMR: δ = 40.1, 57.6, 65.2, 126.3, 127.6, 127.7, 128.1, 128.3, 129.1, 136.9, 137.2, 154.8, 160.1 ppm.

Cbz-*g*Trp-CO-H (4Ze): IR (KBr): $\tilde{\nu}$ = 3435, 3319, 3295, 3062, 3034, 2919, 2893, 1696, 1658, 1544, 1511, 1456, 1393, 1350, 1286, 1268, 1231, 1219, 1187, 1046, 1006, 968, 749, 733, 721, 701, 577, 510 cm^{-1}. MS (ESI+): m/z = 360 [M + Na]$^+$→(MS^2) 315. $C_{19}H_{19}N_3O_3$ (337.38): calcd. C 67.64, H 5.68, N 12.45; found C 67.65, H 5.70, N 12.45. Data for *trans* isomer: ^{1}H NMR: δ = 2.93–3.17 (m, 2 H, Ar-CH_2), 5.04 (s, 2 H, OCH_2), 5.05–5.26 (m, 1 H, *g*CH), 6.91–7.24 (m, 3 H, Ar), 7.24–7.44 (m, 6 H, Ar), 7.54–7.67 (m, 1 H, Ar), 7.93 (br. s, 1 H, NHCOO), 8.01–8.17 (m, 2 H, NHCOH), 10.82 (br. s, 1 H, Ar-NH) ppm. ^{13}C NMR: δ = 30.1, 61.1, 65.4, 109.4, 111.3, 118.0, 118.3, 120.8, 124.0, 127.1, 127.5, 127.8, 128.3, 136.0, 136.7, 155.2, 164.0 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 2.93–3.17 (m, 2 H, Ar-CH_2), 5.01 (s, 2 H, OCH_2), 5.56 (app quint, J = 7.5 Hz, 1 H, *g*CH), 6.91–7.24 (m, 3 H, Ar), 7.24–7.44 (m, 6 H, Ar), 7.54–7.67 (m, 1 H, Ar), 7.70 (br. s, 1 H, NHCOO), 7.98 (dd, J = 1.6, 0.6 Hz, 1 H, HCO), 8.35 (br. d, J = 7.6 Hz, 1 H, N*H*COH), 10.78 (br. s, 1 H, Ar-NH) ppm. ^{13}C NMR: δ = 30.4, 57.1, 65.2, 109.7, 111.2, 118.1, 118.2, 120.7, 123.5, 127.3, 127.6, 127.7, 128.2, 136.0, 136.9, 155.0, 160.3 ppm.

Cbz-*g*Gln-CO-H (4Zg): IR (KBr): $\tilde{\nu}$ = 3435, 3396, 3317, 3285, 3209, 1690, 1661, 1635, 1553, 1519, 1455, 1411, 1386, 1341, 1285, 1265, 1242, 1228, 1187, 1068, 1055, 1012, 635, 578 cm^{-1}. MS (ESI+): m/z = 302 [M + Na]$^+$→(MS^2) 257. $C_{13}H_{17}N_3O_4$ (279.30): calcd. C 55.91, H 6.14, N 15.05; found C 55.93, H 6.11, N 15.01. Data for *trans* isomer: ^{1}H NMR: δ = 1.69–1.92 (m, 2 H, C*H*$_2$CH$_2$CO), 2.02–2.20 (m, 2 H, CH$_2$C*H*$_2$CO), 4.85 (app quint, J = 7.6 Hz, 1 H, *g*CH), 5.03 (s, 2 H, OCH_2), 7.26 (br. s, 2 H, NH_2), 7.30–7.40 (m, 5 H, Ar), 7.85 (br. s, 1 H, NHCOO), 7.98–8.14 (m, 2 H, NHCOH) ppm. ^{13}C NMR: δ = 29.2, 30.7, 60.1, 65.4, 127.5, 127.8, 128.3, 136.8, 155.3, 164.2, 173.4 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 1.69–1.92 (m, 2 H, C*H*$_2$CH$_2$CO), 2.02–2.20 (m, 2 H, CH$_2$C*H*$_2$CO), 5.02 (s, 2 H, OCH_2), 5.27 (app quint, J = 7.6 Hz, 1 H, *g*CH), 6.69 (br. s, 2 H, NH_2), 7.30–7.40 (m, 5 H, Ar), 7.65 (br. s, 1 H, NHCOO), 7.95 (dd, J = 1.6, 0.6 Hz, 1 H, HCO), 8.24 (br. d, J = 7.3 Hz, 1 H, N*H*COH) ppm. ^{13}C NMR: δ = 30.0, 30.9, 56.0, 65.3, 127.6, 127.7, 128.2, 136.9, 154.9, 160.2, 173.5 ppm.

General Procedure for the Synthesis of Formamides 12 Derived from *N*-Protected Dipeptide Acids: *N*-methylmorpholine (0.28 mL, 2.58 mmol) was slowly added to a stirred solution of *N*-protected dipeptide acid **8** (2.50 mmol) in THF (25 mL). After 5 min, isobutyl chloroformate (0.36 mL, 2.75 mmol) was slowly added to the reaction mixture, which was cooled to –15 °C. The stirring was continued for 5 min at the same temperature. After this time, an aqueous solution of KH_2PO_4 (1.4 M, 0.89 mL, 1.25 mmol) was added in one portion followed, after 5 min, by the addition of an aqueous solution of KH_2PO_4 (1.4 M, 8.93 mL, 12.50 mmol) and NaN_3 (0.41 g, 6.25 mmol). After 15 min at –15 °C, the reaction mixture was warmed to 0 °C, and after 15 min, it was warmed to 45 °C and then

stirred for 1.5 h. The reaction mixture was then cooled to room temperature, and the organic phase was separated. Powdered $NaBH_4$ (0.24 g, 6.25 mmol) was rapidly added to the THF solution of carbamoyl azide **10** at room temperature with vigorous stirring. After an additional 45 min, the THF was removed under reduced pressure. The crude residue was dissolved in AcOEt (100 mL), and the resulting solution was washed sequentially with 5% HCl (15 mL), water (15 mL), 5% Na_2CO_3 (15 mL), water (15 mL), and then a saturated brine solution (15 mL). The organic layer was finally dried with Na_2SO_4. After filtration and evaporation in vacuo of the solvent, the crude product was recrystallized from suitable solvents to afford the *N*-protected *N*′-formyl-*gem*-diaminoalkyl derivatives **12** in 72–87% overall yield (see Table 5).

Boc-Val-*g*Trp-CO-H (12Bbe): IR (KBr): $\tilde{\nu}$ = 3411, 3288, 2967, 1667, 1547, 1509, 1457, 1411, 1387, 1366, 1244, 1168, 738 cm^{-1}. MS (ESI+): *m*/*z* = 425 $[M + Na]^+ \rightarrow (MS^2)$ 369, 325. $C_{21}H_{30}N_4O_4$ (402.49): calcd. C 62.67, H 7.51, N 13.92; found C 62.71, H 7.52, N 13.87. Data for *trans* isomer: ^{1}H NMR: δ = 0.74–0.84 [m, 6 H, $(CH_3)_2CH$], 1.39 [s, 9 H, $(CH_3)_3C$], 1.75–2.00 [m, 1 H, $(CH_3)_2CH$], 2.97–3.11 (m, 2 H, Ar-CH_2), 3.79 (app quint, *J* = 7.6 Hz, 1 H, $*CH_{Val}$), 5.33 (app quint, *J* = 7.3 Hz, 1 H, gCH_{Trp}), 6.49 (br. d, *J* = 7.0 Hz, 1 H, NHCOO), 6.92–7.23 (m, 3 H, Ar), 7.28–7.39 (m, 1 H, Ar), 7.53–7.66 (m, 1 H, Ar), 7.95–8.09 (m, 2 H, NHCOH), 8.40 (br. d, *J* = 7.0 Hz, 1 H, $*CH_{Val}CONH$), 10.80 (br. s, 1 H, Ar-NH) ppm. ^{13}C NMR: δ = 17.9, 18.9, 28.0, 29.9, 30.5, 58.7, 59.4 (br. signals), 78.0, 109.2, 111.3, 118.0, 118.3, 120.8, 123.8, 127.0, 136.0, 155.2 (br. signals), 164.1, 171.2 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 0.74–0.84 [m, 6 H, $(CH_3)_2CH$], 1.39 [s, 9 H, $(CH_3)_3C$], 1.75–2.00 [m, 1 H, $(CH_3)_2CH$], 2.97–3.11 (m, 2 H, Ar-CH_2), 3.79 (app quint, *J* = 7.6 Hz, 1 H, $*CH_{Val}$), 5.68 (app quint, *J* = 7.3 Hz, 1 H, gCH_{Trp}), 6.49 (br. d, *J* = 7.0 Hz, 1 H, NHCOO), 6.92–7.23 (m, 3 H, Ar), 7.28–7.39 (m, 1 H, Ar), 7.53–7.66 (m, 1 H, Ar), 7.94 (d, *J* = 1.4 Hz, 1 H, HCO), 8.15 (br. d, *J* = 8.0 Hz, 1 H, N*H*COH), 8.30 (br. d, *J* = 7.6 Hz, 1 H, $*CH_{Val}CONH$), 10.76 (br. s, 1 H, Ar-NH) ppm. ^{13}C NMR: δ = 17.8, 19.0, 28.0, 30.2, 30.5, 55.1, 59.4 (br. signals), 78.0, 109.6, 111.2, 118.1, 118.2, 120.8, 123.3, 127.2, 136.0, 155.2 (br. signals), 160.4, 170.5 ppm.

Boc-Leu-*g*Phe-CO-H (12Bcd): IR (KBr): $\tilde{\nu}$ = 3317, 2959, 2930, 1686, 1666, 1549, 1530, 1510, 1389, 1368, 1275, 1251, 1231, 1173, 1158, 1073, 698, 664 cm^{-1}. MS (ESI+): *m*/*z* = 400 $[M + Na]^+ \rightarrow (MS^2)$ 344, 300. $C_{20}H_{31}N_3O_4$ (377.48): calcd. C 63.64, H 8.28, N 11.13; found C 63.62, H 8.29, N 11.15. Data for *trans* isomer: ^{1}H NMR: δ = 0.77–0.90 [m, 6 H, $(CH_3)_2CH$], 1.20–1.43 [m, 11 H, $(CH_3)_3C$, $CHCH_2$], 1.44–1.64 [m, 1 H, $(CH_3)_2CH$], 2.82–3.05 (m, 2 H, Ph-CH_2), 3.91 (app q, *J* = 7.8 Hz, 1 H, $*CH_{Leu}$), 5.24 (app quint, *J* = 7.9 Hz, 1 H, gCH_{Phe}), 6.71 (br. d, *J* = 7.0 Hz, 1 H, NHCOO), 7.14–7.32 (m, 5 H, Ar), 7.93–8.04 (m, 2 H, NHCOH), 8.30 (br. d, *J* = 7.9 Hz, 1 H, $*CH_{Leu}CONH$) ppm. ^{13}C NMR: δ = 21.4, 22.8, 24.1, 28.1, 39.8, 40.8, 52.7 (br. signals), 59.3, 77.9, 126.3, 128.1, 129.2, 136.8, 155.0 (br. signals), 164.0, 172.3 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 0.77–0.90 [m, 6 H, $(CH_3)_2CH$], 1.20–1.43 [m, 11 H, $(CH_3)_3C$, $CHCH_2$], 1.44–1.64 [m, 1 H, $(CH_3)_2CH$], 2.82–3.05 (m, 2 H, Ph-CH_2), 3.91 (app q, *J* = 7.8 Hz, 1 H, $*CH_{Leu}$), 5.56 (app quint, *J* = 7.9 Hz, 1 H, gCH_{Phe}), 6.71 (br. d, *J* = 7.0 Hz, 1 H, NHCOO), 7.14–7.32 (m, 5 H, Ar), 7.91 (d, *J* = 1.4 Hz, 1 H, HCO), 8.07 (br. d, *J* = 7.9 Hz, 1 H, N*H*COH), 8.30 (br. d, *J* = 7.9 Hz, 1 H, $*CH_{Leu}CONH$) ppm. ^{13}C NMR: δ = 21.4, 22.8, 24.1, 28.1, 39.1, 40.8, 52.7 (br. signals), 55.6, 77.9, 126.2, 128.0, 129.0, 137.0, 155.0 (br. signals), 160.2, 171.7 ppm.

Fmoc-Leu-*g*Ala-CO-H (12Fca): IR (KBr): $\tilde{\nu}$ = 3267, 2955, 2873, 1687, 1667, 1567, 1540, 1520, 1466, 1450, 1387, 1269, 1247, 1224, 1134, 1114, 1035, 737 cm^{-1}. MS (ESI+): *m*/*z* = 446 $[M + Na]^+ \rightarrow (MS^2)$ 401, 375. $C_{24}H_{29}N_3O_4$ (423.51): calcd. C 68.07, H 6.90, N 9.92; found C 68.04, H 6.88, N 9.95. Data for *trans* isomer: ^{1}H NMR: δ = 0.88 [app t, *J* = 5.9 Hz, 6 H, $(CH_3)_2CH$], 1.29 (app t, *J* = 5.9 Hz, 3 H, $gCHCH_3$), 1.36–1.52 (m, 2 H, $CHCH_2$), 1.53–1.74 [m, 1 H, $(CH_3)_2CH$], 3.93–4.13 (m, 1 H, $*CH_{Leu}$), 4.14–4.41 (m, 3 H, $CHCH_2O$), 5.21 (app sext, *J* = 7.6 Hz, 1 H, gCH_{Ala}), 7.22–7.49 (m, 5 H, Ar, NHCOO), 7.71 (app d, *J* = 6.5 Hz, 2 H, Ar), 7.88 (app d, *J* = 7.0 Hz, 2 H, Ar), 8.04–8.23 (m, 2 H, NHCOH), 8.30 (br. d, *J* = 7.0 Hz, 1 H, $*CH_{Leu}CONH$) ppm. ^{13}C NMR: δ = 20.3, 21.3, 22.9, 24.0, 40.7, 46.6, 52.9 (br. signals), 54.2, 65.4, 119.9, 125.1, 126.8, 127.4, 140.6, 143.6, 143.8, 155.7 (br. signals), 164.0, 172.0 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 0.88 [app t, *J* = 5.9 Hz, 6 H, $(CH_3)_2CH$], 1.29 (app t, *J* = 5.9 Hz, 3 H, $gCHCH_3$), 1.36–1.52 (m, 2 H, $CHCH_2$), 1.53–1.74 [m, 1 H, $(CH_3)_2CH$], 3.93–4.13 (m, 1 H, $*CH_{Leu}$), 4.14–4.41 (m, 3 H, $CHCH_2O$), 5.52 (app sext, *J* = 7.6 Hz, 1 H, gCH_{gAla}), 7.22–7.49 (m, 5 H, Ar, NHCOO), 7.71 (app d, *J* = 6.5 Hz, 2 H, Ar), 7.88 (app d, *J* = 7.0 Hz, 2 H, Ar), 7.92 (d, *J* = 1.2 Hz, 1 H, HCO), 8.04–8.23 (m, 2 H, N*H*COH, $*CH_{Leu}CONH$) ppm. ^{13}C NMR: δ = 20.6, 21.3, 22.9, 24.0, 40.7, 46.6, 50.8, 52.9 (br. signals), 65.4, 119.9, 125.1, 126.8, 127.4, 140.6, 143.6, 143.8, 155.7 (br. signals), 159.9, 171.3 ppm.

Fmoc-Leu-*g*Phg-CO-H (12Fch): IR (KBr): $\tilde{\nu}$ = 3292, 2955, 2934, 2844, 1683, 1659, 1643, 1542, 1516, 1450, 1397, 1322, 1283, 1265, 1244, 1208, 1128, 1030, 739, 697, 667 cm^{-1}. MS (ESI+): *m*/*z* = 508 $[M + Na]^+ \rightarrow (MS^2)$ 463, 375. $C_{29}H_{31}N_3O_4$ (485.58): calcd. C 71.73, H 6.43, N 8.65; found C 71.74, H 6.41, N 8.61. Data for *trans* isomer: ^{1}H NMR: δ = 0.88 [app t, *J* = 6.8 Hz, 6 H, $(CH_3)_2CH$], 1.34–1.73 (m, 3 H, $CHCH_2$), 4.01–4.20 (m, 1 H, $*CH_{Leu}$), 4.21–4.40 (m, 3 H, $CHCH_2O$), 6.31 (app t, *J* = 8.5 Hz, 1 H, gCH_{Phg}), 7.23–7.50 (m, 10 H, Ar, NHCOO), 7.72 (app d, *J* = 7.0 Hz, 2 H, Ar), 7.88 (app d, *J* = 6.8 Hz, 2 H, Ar), 8.27 (d, *J* = 11.2 Hz, 1 H, HCO), 8.44 (br. t, *J* = 10.2 Hz, 1 H, N*H*COH), 8.52–8.72 (m, 1 H, $*CH_{Leu}CONH$) ppm. ^{13}C NMR: δ = 21.3, 22.8, 24.1, 40.6, 46.6, 53.1 (br. signals), 60.1, 65.5, 119.9, 125.1, 126.2, 126.9, 127.4, 127.8, 128.2, 139.0, 140.6, 143.6, 143.8, 155.7 (br. signals), 164.5, 172.2 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 0.88 [app t, *J* = 6.8 Hz, 6 H, $(CH_3)_2CH$], 1.34–1.73 (m, 3 H, $CHCH_2$), 4.01–4.20 (m, 1 H, $*CH_{Leu}$), 4.21–4.40 (m, 3 H, $CHCH_2O$), 6.66 (app t, *J* = 8.2 Hz, 1 H, gCH_{Phg}), 7.23–7.50 (m, 10 H, Ar, NHCOO), 7.72 (app d, *J* = 7.0 Hz, 2 H, Ar), 7.88 (app d, *J* = 6.8 Hz, 2 H, Ar), 8.10 (d, *J* = 1.2 Hz, 1 H, HCO), 8.52–8.72 (m, 2 H, N*H*COH, $*CH_{Leu}CONH$) ppm. ^{13}C NMR: δ = 21.3, 22.8, 24.1, 40.6, 46.6, 53.1 (br. signals), 55.6, 65.5, 119.9, 125.1, 125.9, 126.9, 127.4, 127.5, 128.1, 139.8, 140.6, 143.6, 143.8, 155.7 (br. signals), 160.2, 171.5 ppm.

Fmoc-Phe-*g*Ala-CO-H (12Fda): IR (KBr): $\tilde{\nu}$ = 3280, 2870, 1690, 1673, 1652, 1566, 1540, 1521, 1450, 1392, 1287, 1262, 1249, 1223, 1126, 1086, 1035, 756, 740, 708, 666, 514 cm^{-1}. MS (ESI+): *m*/*z* = 480 $[M + Na]^+ \rightarrow (MS^2)$ 435, 409. $C_{27}H_{27}N_3O_4$ (457.53): calcd. C 70.88, H 5.95, N 9.18; found C 70.91, H 5.99, N 9.16. Data for *trans* isomer: ^{1}H NMR: δ = 1.31 (app t, *J* = 6.5 Hz, 3 H, CH_3), 2.78 and 3.00 (AB of ABX, *J* = 13.8, 10.3, 4.4 Hz, 2 H, Ph-CH_2), 4.07–4.33 (m, 4 H, $CHCH_2O$, $*CH_{Phe}$), 5.24 (app sext, *J* = 7.0 Hz, 1 H, gCH_{Ala}), 7.12–7.50 (m, 10 H, Ar, NHCOO), 7.56–7.70 (m, 2 H, Ar), 7.86 (app d, *J* = 7.0 Hz, 2 H, Ar), 7.98 (br. t, *J* = 10.2 Hz, 1 H, N*H*COH), 8.17 (d, *J* = 11.5 Hz, 1 H, HCO), 8.48 (br. d, *J* = 7.3 Hz, 1 H, $*CH_{Phe}CONH$) ppm. ^{13}C NMR: δ = 20.4, 37.3, 46.5, 54.3, 55.8 (br. signals), 65.5, 119.9, 125.0, 126.1, 126.9, 127.4, 127.8, 129.1, 137.7, 140.5, 143.5, 143.6, 155.5 (br. signals), 164.0, 171.0 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 1.31 (app t, *J* = 6.5 Hz, 3 H, CH_3), 2.78 and 3.00 (AB of ABX, *J* = 13.8, 10.3, 4.4 Hz, 2 H, Ph-CH_2), 4.07–4.33 (m, 4 H, $CHCH_2O$, $*CH_{Phe}$), 5.55 (app sext, *J* = 7.0 Hz, 1 H, gCH_{Ala}), 7.12–7.50 (m, 10 H, Ar,

NHCOO), 7.56–7.70 (m, 2 H, Ar), 7.86 (app d, J = 7.0 Hz, 2 H, Ar), 7.94 (d, J = 1.2 Hz, 1 H, HCO), 8.23 (br. d, J = 7.6 Hz, 1 H, N*H*COH), 8.30 (br. d, J = 7.3 Hz, 1 H, *CH_{Phe}CON*H*) ppm. ^{13}C NMR: δ = 20.6, 37.4, 46.5, 51.0, 55.8 (br. signals), 65.5, 119.9, 125.1, 126.0, 126.9, 127.4, 127.8, 129.1, 137.9, 140.5, 143.5, 143.6, 155.5 (br. signals), 159.9, 170.4 ppm.

Cbz-Phe-*g*Ala-CO-H (12Zda): IR (KBr): $\tilde{\nu}$ = 3285, 3026, 1685, 1668, 1645, 1556, 1535, 1518, 1454, 1395, 1315, 1297, 1258, 1217, 1131, 1083, 1042, 745, 695, 674, 520 cm^{-1}. MS (ESI+): m/z = 392 $[M + Na]^+ \rightarrow (MS^2)$ 347, 321. $C_{20}H_{23}N_3O_4$ (369.42): calcd. C 65.03, H 6.28, N 11.37; found C 65.00, H 6.30, N 11.34. Data for *trans* isomer: ^{1}H NMR: δ = 1.31 (app t, J = 6.3 Hz, 3 H, CH_3), 2.73 and 2.99 (AB of ABX, J = 13.5, 10.6, 4.1 Hz, 2 H, Ph-CH_2), 4.12–4.34 (m, 1 H, *CH_{Phe}), 4.95 (s, 2 H, CH_2O), 5.23 (app sext, J = 7.0 Hz, 1 H, *g*CH_{Ala}), 7.10–7.45 (m, 11 H, Ar, NHCOO), 7.99 (br. t, J = 10.1 Hz, 1 H, N*H*COH), 8.16 (d, J = 11.5 Hz, 1 H, HCO), 8.48 (br. d, J = 7.0 Hz, 1 H, *CH_{Phe}CON*H*) ppm. ^{13}C NMR: δ = 20.4, 37.3, 54.3, 55.8 (br. signals), 65.1, 126.1, 127.3, 127.5, 127.9, 128.1, 129.1, 136.9, 137.7, 155.7 (br. signals), 164.1, 171.1 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 1.31 (app t, J = 6.3 Hz, 3 H, CH_3), 2.73 and 2.99 (AB of ABX, J = 13.5, 10.6, 4.1 Hz, 2 H, Ph-CH_2), 4.12–4.34 (m, 1 H, *CH_{Phe}), 4.95 (s, 2 H, CH_2O), 5.53 (app sext, J = 7.0 Hz, 1 H, *g*CH_{Ala}), 7.10–7.45 (m, 11 H, Ar, NHCOO), 7.94 (d, J = 1.2 Hz, 1 H, HCO), 8.23 (br. d, J = 7.6 Hz, 1 H, N*H*COH), 8.31 (br. d, J = 7.0 Hz, 1 H, *CH_{Phe}CON*H*) ppm. ^{13}C NMR: δ = 20.6, 37.4, 51.0, 55.8 (br. signals), 65.1, 126.0, 127.3, 127.5, 127.9, 128.1, 129.1, 136.9, 137.9, 155.7 (br. signals), 160.0, 170.4 ppm.

Cbz-Phe-*g*Phe-CO-H (12Zdd): IR (KBr): $\tilde{\nu}$ = 3296, 3025, 1689, 1664, 1647, 1556, 1535, 1515, 1497, 1455, 1392, 1309, 1256, 1220, 1088, 1074, 1042, 1026, 742, 700, 536, 519 cm^{-1}. MS (ESI+): m/z = 468 $[M + Na]^+ \rightarrow (MS^2)$ 423, 321. $C_{26}H_{27}N_3O_4$ (445.52): calcd. C 70.10, H 6.11, N 9.43; found C 70.14, H 6.10, N 9.41. Data for *trans* isomer: ^{1}H NMR: δ = 2.63–3.05 (m, 4 H, 2 Ph-CH_2), 4.14–4.35 (m, 1 H, *CH_{Phe}), 4.96 (s, 2 H, CH_2O), 5.27 (app quint, J = 7.6 Hz, 1 H, *g*CH_{Phe}), 7.12–7.42 (m, 16 H, Ar, NHCOO), 7.96–8.06 (m, 2 H, NHCOH), 8.53 (br. d, J = 7.0 Hz, 1 H, *CH_{Phe}CON*H*) ppm. ^{13}C NMR: δ = 37.3 (br. signals), 40.1, 55.9 (br. signals), 59.5, 65.1, 126.0, 126.2, 127.2, 127.4, 127.8, 128.0, 128.1, 128.9, 129.2, 136.7, 136.9, 137.6, 155.5 (br. signals), 163.9, 171.0 ppm. Data for *cis* isomer: ^{1}H NMR: δ = 2.63–3.05 (m, 4 H, 2 Ph-CH_2), 4.14–4.35 (m, 1 H, *CH_{Phe}), 4.96 (s, 2 H, CH_2O), 5.61 (app quint, J = 7.6 Hz, 1 H, *g*CH_{Phe}), 7.12–7.42 (m, 16 H, Ar, NHCOO), 7.95 (d, J = 1.2 Hz, 1 H, HCO), 8.23–8.39 (m, 2 H, N*H*COH, *CH_{Phe}CON*H*) ppm. ^{13}C NMR: δ = 37.3 (br. signals), 39.7, 55.7, 55.9 (br. signals), 65.1, 125.9, 126.1, 127.2, 127.4, 127.8, 127.9, 128.1, 128.9, 129.0, 136.8, 136.9, 137.8, 155.5 (br. signals), 160.2, 170.5 ppm.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra for all prepared compounds.

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