(±)-**4a**, 125108-97-6; (±)-**46**, 125109-01-5; (±)-**5**, 125108-98-7; (±)-**6a**, 125108-99-8; (±)-**6b**, 125109-00-4; **14**, 125109-04-8; **15a**, 16686-11-6; (±)-**15b**, 125109-03-7; **16a**, 125109-05-9; (±)-**16b**, 125109-02-6; **17**, 125109-06-0; DL-**18**, 125137-41-9; DL-**19**, 125109-07-1; **20**, 125109-08-2; (±)-**21**, 125109-09-3; DL-**22**, 125109-10-6; **23**, 125109-11-7; **24**, 125137-86-2; (±)-**25**, 125109-12-8; DL-**26**, 125109-13-9; **27**, 125109-14-0; **28**, 125109-15-1; (±)-**29**, 125109-16-2; **30**, 125137-87-3; (±)-**34a**, 125109-18-4; (±)-**34b**, 125109-17-3; $Br(CH_2)_3COOMe$, 4897-84-1; $Br(CH_2)_3CH(OMe)_2$, 24157-02-6.

Benzotriazole-Assisted Synthesis of Monoacyl Aminals and Their Peptide Derivatives

Alan R. Katritzky,* Laszlo Urogdi, and Annie Mayence

Department of Chemistry, University of Florida, Gainesville, Florida 32611

Received July 18, 1989

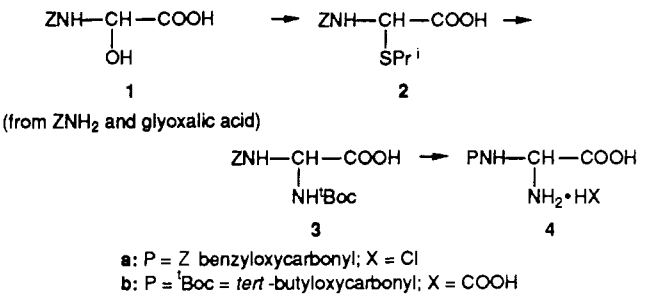
Adducts 8–11, derived from benzotriazole (**7**), an aldehyde (**6**), and an amide (**5**), react with ammonia to give various monoacylated aminals (**12–14**) and "*gem*-peptide"[2a] derivatives (**15**) in a novel, convenient route, useful for peptide analogue syntheses and studies.

Reversing one or more of the amide groups (i.e. CHRCONH to CHRNHCO) of a linear peptide gives a so-called "partially modified retro isomer" and represents an important strategy in peptide analogue research.[1a,2] The modified sequence requires both a malonic unit and a (much less easily available) α,α-diamino moiety. Such α,α-diamino units have been synthesized by Curtius-[1,3,5] or Hoffmann-type[2,3,4] rearrangements of protected amino acid derivatives. The appropriate "*gem*-peptides" are usually also synthesized by one of these degradations of a protected peptide amide,[2a-c,4] and only in a few cases have monoprotected aminals ($PNHCH(R)NH_2$) been used as (or synthesized for) building units for their preparation.[1a-b,5,6] In all cases, these monoprotected aminals have been synthesized via unsymmetrically bis-protected derivatives. Recently, α-carboxyl-substituted compounds were synthesized by Bock and co-workers[6] from α-hydroxy-*N*-(benzyloxycarbonyl)glycine (**1**) in three-step sequences as shown in Scheme I for **4a** and **4b**. These α-carboxyl-substituted aminals **4** are *gem*-analogues of aminomalonic acid derivatives, which are of only minor importance in peptide sequences.

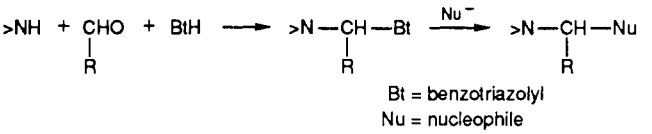
Earlier we reported[7] a convenient synthesis of compounds of type >NCH(R)X mediated by benzotriazole via the general route of Scheme II. More recently, this methodology with glyoxylic acid as the oxo component (R = COOH) and ammonia as the nucleophile allowed a convenient synthesis of monoacyl-α-aminoglycines of type **4**.[8]

We have now found that in adducts 8–11 (Scheme III), formed from various amides (including protected amino acid amides for compounds **11**) and aldehydes, the benzotriazole moiety can be replaced by NH_3 providing (i) a convenient and versatile method for the preparation of various simple α-substituted monoacyl aminals **12–14**, and (ii) a novel synthetic route to "*gem*-dipeptides" **15**.[2a]

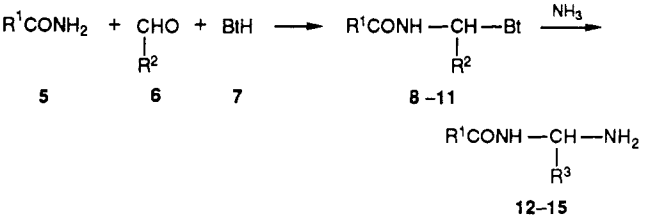
Scheme I



Scheme II



Scheme III[a]



[a] For designating of R^1, R^2, and R^3 see Tables I–IV (all can be alkyl or aryl, additionally R^1 can be OR or $RCONHCH_2$; R^2 can be CO_2H or CO_2R; R^3 can be CO_2H or $CONH_2$).

(1) (a) Goodman, M.; Chorev, M. *Acc. Chem. Res.* **1979**, *12*, 1. (b) DeBons, F. E.; Loudon, G. M. *J. Org. Chem.* **1980**, *45*, 1703. (c) Loudon, G. M.; Almond, M. R.; Jacob, J. N. *J. Am. Chem. Soc.* **1981**, *103*, 4508.

(2) (a) Chorev, M.; Shavitz, R.; Goodman, M.; Minick, S.; Guillemin, *Science (Washington D.C.)* **1979**, *204*, 1210. In the paper (Table I) the authors "suggest the following prefixes: g- for *gem*-diamino alkyl corresponding to the amino acid residue denoted", (e.g. g-Phe for -NH-CH-(Bzl)-NH- fragment). Correspondingly, we apply the "*gem*-peptide" terminology for peptides containing such "g-" units in the terminal position. (b) Verland, M. S.; Fuller, W. D.; Goodman, M. Eur. Pat. *Appl.*, EP (128,654, 1984; *Chem. Abstr.* **1984**, *102*, 185492c. (c) Fuller, W. D.; Goodman, M.; Verlander, M. S. *J. Am. Chem. Soc.* **1985**, *107*, 5821.

(3) Moutevelis-Minakakis, P.; Photaki, I. *J. Chem. Soc., Perkin Trans. 1* 1985, 2277.

(4) Pallai, P.; Goodman, M. *J. Chem. Soc., Chem. Commun.* **1982**, 280.

(5) Chorev, M.; Willson, C. G.; Goodman, M. *J. Am. Chem. Soc.* **1977**, *99*, 8075.

(6) Bock, M. G.; DiPardo, R. M.; Freidinger, R. M. *J. Org. Chem.* **1986**, *51*, 3718.

(7) (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 805. (b) Katritzky, A. R.; Yannakopoulou, K.,; Lue, P.; Rasala, D.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 225. (c) Katritzky, A. R.; Drewniak, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2339. (d) Katritzky, A. R.; Drewniak, M. *Tetrahedron Lett.* **1988**, *29*, 1755. (e) Katritzky, A. R.; Urogdi, L.; Mayence, A. *Synthesis* **1989**, *323*.

(8) Katritzky, A. R.; Urogdi, L.; Mayence, A. *J. Chem. Soc., Chem. Commun.* **1989**, 337.

0022-3263/90/1955-2206$02.50/0

Table I. Preparation of Benzotriazole Adducts 8–10 $R^1CONHCH(R^2)Bt$

no.	R^1	R^2	yield,[a] %	cryst solvent	mp, °C	R_f[b] (TLC)	analysis (calcd/found) C	H	N
8a	BzlO	H	80	MeOH	124	0.7/BM	63.8/64.1	5.0/5.0	19.9/20.1
8b	BzlO	Pr^n	90	PE	72–73	0.8/BM	66.4/66.6	6.5/6.1	17.2/17.4
8c	BzlO	Pr^i	75	Et_2O	170–172	0.7/BM	66.4/66.0	6.5/6.4	17.2/17.1
8d	BzlO	Bu^i	85 (60)	Et_2O	121–123[c]	0.7/BM	67.2/67.3	6.8/6.6	16.5/16.8
8e	BzlO	Ph	87 (60)	PE	130–131[d]	0.7/BM[e]	70.4/70.1	5.1/5.0	15.6/15.4
9a	Me	COOEt	72	Et_2O	146–147	0.6/BA	55.0/55.2	5.4/5.4	21.4/21.3
9b	Ph	COOEt	74	Et_2O	126–127	0.7/BA	63.0/62.9	5.0/4.9	17.3/17.2
9c	BzlO	COOEt	70[f]	Et_2O	99–101	0.7/BA	61.0/61.1	5.1/5.1	15.8/15.7
10a	Me	COOH	91	Et_2O	193–195	0.2/P1	51.3/50.9	4.3/4.3	23.9/23.7
10b	Ph	COOH	90	Et_2O	193–194	0.4/P1	60.8/60.6	4.1/4.1	18.9/18.9
10c	BzlO	COOH	78	Et_2O	162–164	0.2/P1	58.9/58.8	4.3/4.4	17.2/16.7
10d	^tBuO	COOH	40[g]	Et_2O	133–134	0.2/P2	53.4/53.4	5.5/5.6	19.2/19.3

[a] If an oil was isolated first, the yields in parentheses refer to the solid product. [b] See General Experimental. [c] Lit.[9] mp 121–123 °C. From the mother liquor the benzotriazol-2-yl isomer was isolated with hexanes: R_f = 0.8/BM; mp 93–94 °C; analysis 67.2/67.1, 6.8/6.6, 16.5/16.5; ^{13}C NMR (75 MHz, in $CDCl_3$, δ ppm) 135.7, 126.5, 118.2 (Bt), 71.4 (N-CH-N), 67.2 (Z-CH_2), 44.0, 24.4, 22.1, 22.0 (Bu^i) signals. Signals of the 1-yl isomer are also present, because of the fast isomerization in solution. Overlapping prevents assignation of the ^1H NMR spectrum. [d] Pure benzotriazol-1-yl isomer (see Discussion). Lit.[9] mp 115–117 °C, for a mixture of 1-yl and 2-yl isomers. [e] Partial "on-plate" decomposition observed. [f] After usual workup (see Experimental) 60% product is isolated; evaporation of the ethereal mother liquor followed by trituration of the residue with Pr^i_2O gives an additional 10%. [g] Isolated by extraction into aqueous $NaHCO_3$, followed by acidification, reextraction into ether and evaporation; the resulting foam solidifies with hexanes and is filtered with ether.

Table II. Preparation of Amino Acid–Benzotriazole Adducts 11 $R^1CONHCH(R^2)Bt$

no.	R^1CO[b]	R^2	yield,[b] %	cryst solvent	mp,[c] °C	R_f[d] (TLC)	analysis[c] (calcd/found) C	H	N
11a	Bz-Gly	Pr^i	74 (s)	EtOAc	180–183	0.5/BM	64.9/64.5	6.0/6.0	19.9/19.8
11b	Z-L-Val	Bu^i	80 (o)	–	foam	0.6/BM	65.9/65.8	7.1/7.3	16.0/15.5
11c	Z-iLeu	Pr^i	50 (s)	Et_2O	140–149	0.7/HA	65.9/65.6	7.1/7.2	16.0/15.6
11d	Z-Phg	Bu^i	88 (o)	Et_2O	164–170[e]	0.7/BM	68.8/68.9	6.2/6.3	14.8/14.5
11e	Z-Phe	Pr^i	73 (s)	EtOH	178–183[e]	0.6/HE	68.8/68.7	6.2/6.2	14.8/14.8
11f	Bz-Gly	COOEt	70 (s)	Et_2O	109–112	0.6/BA	59.8/59.7	5.0/5.0	18.4/18.3
11g	Z-Gly	COOEt	70 (s)	$^iPr_2O$	115–116	0.7/BA	58.4/58.4	5.1/5.2	17.0/16.6
11h	Z-Gly	COONa	42 (s)	–	132–142[f]	0.2/P2	51.1/51.0	4.3/4.6	16.5/16.4

[a] Abbreviations: Bz = PhCO; Z = $PhCH_2OCO$; Gly = glycyl; Val = valyl; iLeu = isoleucyl; Phg = *C*-phenylglycyl; Phe = phenylalanyl. The starting amino acid derivatives are racemic, except for **11b**. The starting Z-iLeuNH_2 is furthermore a ~1:1 α/β diastereomeric mixture. [b] Yields for crude, TLC pure products, giving clean NMR spectra, but duplicated signals for the diastereomeric mixtures **11b–e**: (s) = solid, (o) = oil. [c] Mp and analysis given for the same, crude (**11a–c,f–h**) or crystallized, analytically pure (in the case of **11d–e** diastereohomogeneous) products. [d] See General Experimental. [e] Mp and analysis of crystallized, diastereopure product. [f] Crude, dihydrate.

Preparation of Adducts 8–11 (Tables I and II). The condensation of amides and benzotriazole with aliphatic and aromatic aldehydes has been reported.[7c] Extension of this reaction to include carbamates as the amide component[9] (i.e. $BzlOCONH_2$ for **8a–e**) requires an acidic catalyst; *p*-toluenesulfonic acid in toluene is used, with the usual azeotropic removal of the water formed, to give good yields with various aldehydes (see Table I). In all reactions, the formation of a minor side product was observed (TLC). This was isolated in the case of **8d** and proved to be the benzotriazol-2-yl isomer of the major product 1-yl derivative (see footnote *b* in Table I). The isolated 2-yl isomer slowly isomerized in $CDCl_3$ solution to give an equilibrium mixture which is dominated by the benzotriazol-1-yl isomer. Adduct **8e**, obtained previously[9] as a mixture of isomers, has been isolated as the pure 1-yl isomer, consequently exhibiting a higher melting point than reported for the mixture (see Table I).

Reactions with ethyl glyoxylate as the aldehyde component take place under the same conditions (in toluene with *p*-toluenesulfonic acid catalyst in a Dean–Stark apparatus) to give the expected adducts **9a–c**; however, use of an excess of the ethyl glyoxylate is necessary to obtain good (70–75%) yields (Table I).

Condensations of glyoxylic acid with amides and benzotriazole proceed more easily. No catalyst is needed, and the reactions can be carried out at a lower temperature (i.e. in refluxing benzene, with a Dean–Stark adapter) using an equimolar ratio of the reactants to give adducts **10a–d**. The isolation of products **10a–c** is very convenient since the sparingly soluble, solid products precipitate and can be filtered off from the reaction mixture. Compound **10d** was found to be relatively unstable under the conditions employed and was isolated after a short reaction time (30 min) by an extractive workup procedure (see the Experimental Section).

Protected amino acid amides also form adducts with aldehydes and benzotriazole (**11a–e**, Table II). The reaction conditions, which depend principally on the nature of the aldehyde component, are the same as for the corresponding adducts **8** and **9**. When excess benzotriazole was used (**11b,e**), it was removed during the workup procedure by alkaline (K_2CO_3) extraction. In cases **11b–e**, the crude products are diastereomeric mixtures; no dominant asymmetric induction was observed in formation of the new chiral center. However, the separation of pure diastereomers was achieved in the cases of **11d** and **11e**. Surprisingly, the pure diastereomer of **11e** was obtained in much higher yield (85%) than expected from the NMR analysis of the crude product (~1:1 mixture), obviously due to preferred crystallization–equilibration phenomena. Condensations of the protected amino acid amides with glyoxylic acid and benzotriazole gave only poor results; adduct **11h** was more conveniently obtained by hydrolysis of the appropriate ester **11g**.

Reactions of Adducts 8–11 with Ammonia (Tables III and IV). These reactions were carried out in satu-

(9) Katritzky, A. R.; Yannakopoulou, K., submitted for publication in *Synthesis*.

Table III. Preparation of Monoacyl Aminals 12–14 $R^1CONHCH(R^3)NH_2$

no.	R^1	R^3	yield, %	cryst solvent	mp, °C	R_f[a] (TLC)	analysis (calcd/found) C	H	N
12a[b]	BzlO	H	77	EtOAc	121–124	0.3/BM	54.5/54.4	5.7/5.7	7.9/7.8
12b[b]	BzlO	Pr^n	74	EtOAc	112–113	0.5/BM	57.8/57.9	6.6/6.7	7.1/7.1
12c[b]	BzlO	Pr^i	66	EtOAc	125	0.4/BM	57.8/57.4	6.6/6.6	7.1/7.0
12d[b]	BzlO	Bu^i	77	EtOAc	113–114	0.5/BM	58.8/58.8	6.9/6.9	6.9/6.8
12e[b]	BzlO	Bzl	63	EtOAc	120–121	0.6/BM	62.4/62.1	5.9/5.9	6.3/6.3
13a	Me	$CONH_2$	91	MeOH	130–132[c]	0.4/CM	36.6/36.3	6.9/6.7	32.0/32.1
13b	Ph	$CONH_2$	86	Et_2O	130[d]	0.6/CM	56.0/56.2	5.7/5.7	21.7/21.7
13c[e]	BzlO	$CONH_2$	37	*e*	113	0.6/CM	53.8/53.6	5.9/5.8	18.8/18.8
14a	BzlO	COOH	70	Me_2CO	142–144[f]	-	53.6/53.5	5.4/5.4	12.5/12.9

[a] See General Experimental. [b] Yield, mp, and analysis given for the isolated tosylate salt. [c] The tosylate salt was also prepared in EtOAc; after purification by washing with MeOH, correct C, H, N analysis was obtained (C, 43.6/43.4, H, 5.6/5.6, N, 13.9/14.0). The salt gradually decomposes while heating; no mp could be detected. [d] Flash melting point (see General Experimental). [e] $CHCl_3$–MeOH–hexanes. [f] Lit.[6] mp 135 °C.

Table IV. Preparation of "*gem*-Dipeptides" 15 $R^1CONHCH(R^3)NH_2$

no.	st.[a]	R^1CO[b]	R^3	yield,[c] %	cryst solvent[d]	mp,[d] °C	R_f[e] (TLC)	analysis[d] (calcd/found) C	H	N
15a	A	Bz-Gly	Pr^i	75 (s)	EtOAc	132–133[f,g]	0.2/BM	57.0/56.6	6.5/6.4	10.0/10.1
15b	B	Z-L-Val	Bu^i	86 (s)	Et_2O	130[h,i]	0.3/BM	64.4/64.1	8.7/8.5	12.5/12.4
15c	B	Z-iLeu	Pr^i	87 (s)	EtOAc	135[f,h,j]	0.4/BM	59.1/59.0	7.3/7.2	8.3/7.9
15d	B	Z-Phg	Bu^i	78 (o)[k]	*l*	129–130[f]	0.3/HA	62.1/	6.5/6.6	7.8/7.5
15e	C	Z-Phe	Pr^i	98 (o)	Et_2O	105[h]	0.3/BM	68.3/68.2	7.4/7.5	11.4/11.1
15f	A	Bz-Gly	$CONH_2$	98 (s)	Et_2O	190–194	0.5/CM	52.8/52.9	5.6/5.6	22.4/22.5
15g	A	Z-Gly	$CONH_2$	85 (s)	MeOH	124–125	0.4/CM	51.2/51.1	6.1/5.8	19.9/20.1
15h	A	Z-Gly	COOH	48 (s)	H_2O	159–160	0.1/P2	51.2/	5.4/5.2	14.9/14.6

[a] Stereocomposition of the starting material 11: A = racemate; B = crude adduct, ~1:1 mixture of diastereomers; C = crystallized adduct, single diastereomer. [b] See footnote *a* under Table II. [c] Yields for crude, TLC pure products, giving clean NMR spectra, but duplicated signals for the diastereomeric mixtures **15b–e**; (s) solid, (o) = oil. [d] Cryst solvent, mp, and analysis given for the same, pure (in the case of **15b–e** diastereohomogeneous) products (base or tosylate salt). [e] See General Experimental. [f] Mp and analysis for tosylate salt. [g] Mp of the free base: 125 °C.[h] [h] Flash mp (see General Experimental). [i] Mp of the tosylate salt: 110–112 °C. [j] Mp of the free base: 122 °C.[h] [k] The spectra of the crude product indicates presence of a minor impurity, probably 1-(benzyloxycarbonyl)-2-isobutyl-5-phenylimidazolidin-4-one. [l] Et_2O–EtOAc, 4:1.

rated alcoholic or aqueous NH_3 solution usually at room temperature. In the case of the ethyl glyoxylate adducts (**9,11g,h**) simultaneous amidation of the ester function occurs along with the displacement of the benzotriazole moiety. The required conditions depend strongly on the nature of the acyl (R^1CO) and R^2 substituents. Increasing reactivity was observed for R^1 = Me < amidoalkyl < Ph < BzlO, and for R^2 = COOH ≪ alkyl < COOEt < Ph substituents. Following the reactions by TLC suggests that they lead to equilibria: small amounts of unreacted starting materials were often observed even after long reaction times. In the reactions of adducts lacking an acidic side chain, the addition of finely powdered K_2CO_3 highly increased the rate and led to complete reaction, presumably due to removal of the side product benzotriazole from the solution. From among the less reactive R^2 = COOH derivatives only the benzyloxycarbonyl compound (**10c**) gave the corresponding aminal **14a**. The others (**10a,b,d**) required several weeks for complete conversion (i.e. until no more starting compound was detected by TLC), after which only unidentifiable, poorly soluble products could be isolated.

The separation of the products from benzotriazole depends on their solubility. In the aqueous case a simple filtration (**12c**), in most of the other cases evaporation and isolation with an appropriate solvent, afforded solid products in a practically pure state. The side product benzotriazole was removed in the mother liquor. In the case of the highly soluble compounds (**12a–e**), removal of benzotriazole was achieved by stirring the ethereal solution with solid K_2CO_3.

The stereochemistry of the Bt/NH_3 displacement reaction was investigated in the case of preparation of "*gem*-dipeptide" **15e**. Diastereohomogeneous starting adduct **11e** was used, and the crude product, obtained in nearly quantitative yield (i.e. no separation of the potential diastereomers occurred), was investigated by reverse-phase HPLC under similar conditions as used, for example, by Conradi and Burton[10] for separation of Boc-Phe-Phe-Gly diastereomers. Peak integration values revealed a 60:40 ratio in favor of the more hydrophobic component. A similar conclusion is obtained from the ^1H NMR spectrum of the crude product: ~3:2 duplication of the Phe-CON*H* proton signal can be observed at 6.5 and 6.2 ppm. Finally, single diastereomer Z-Phe-gVal was prepared[4] from Z-L-Phe-L-Val NH_2[11] and was compared by ^1H and ^{13}C NMR analyses with **11e** proving clearly that the latter is a diastereomeric mixture. Thus, we can conclude that the displacement reaction proceeded in this case with almost complete racemization, probably due to a S_N1-type reaction mechanism.

Because of the lack of stereoretention, all other bis-chiral adducts (**11b–d**) were subjected to the reaction with NH_3 as crude, diastereomeric mixtures and resulted in mixtures of diastereomer aminals **15**. However, separation of the diastereomers occurred in each case during purification (crystallization or salt formation) leading to single diastereomers as final products (see Table IV).

The stability of the aminals **12–15** depends on their structure. The zwitterionic amino acids (**14**) are stable at room temperature, but the others show a tendency to form dimer derivatives $(R^1CONHCHR^3)_2NH$. This tendency is, again, highly dependent on the nature of the R^1 and R^3 substituents, just as is the rate of the Bt/NH_3 displacement reaction. For example, while the benzoyl derivative **13b** does not dimerize during preparation in homogeneous

(10) Conradi, R. A.; Burton, P. S. *Int. J. Pept. Res.* **1989**, *33*, 373.
(11) Kuhl, P.; Zapevalova, N. P.; Könnecke, A.; Jakubke, H.-D. *Monatsh.* **1983**, *114*, 343.

Table V. ^{1}H NMR Spectral Data of Novel Benzotriazole Adducts 8–10 R^{1}CONHCH(R^2)Bt

no.	solvent	inst[a]	Bt signals	NCHN	R^2	CONH	R^1
8a	$CDCl_3$	A	8.1–7.7 (2 H, m), 7.6–7.2 (2 H, m)[b]	6.0 (d)[b]	6.0 (d)[b]	6.5 (t)	7.6–7.2 (5 H, m),[b] 5.1 (2 H, s)
8b	$CDCl_3$	B	8.1–7.8 (2 H, m), 7.6–7.0 (2 H, m)[b]	6.5 (m)	2.5–2.2 (2 H, m), 1.5–1.1 (2 H, m), 1.0–0.8 (3 H, m)	7.5–7.0 (m)[b]	7.6–7.2 (5 H, m),[b] 5.05 (2 H, AB q)
8c	$CDCl_3$	B	8.05 (1 H, d), 7.77 (1 H, d), 7.55–7.1 (2 H, m)[b]	6.1 (t)	2.85–2.6 (1 H, m), 1.2 (3 H, d), 0.85 (3 H, d)	6.3 (d)	7.55–7.1 (5 H, m),[b] 5.05 (2 H, AB q)
9a	$CDCl_3$	C	8.03 (1 H, d), 7.91 (1 H, d), 7.55 (1 H, t), 7.41 (1 H, t)	7.27 (d)	4.32 (2 H, q), 1.23 (3 H, t)	8.0 (d)	2.08 (s)
9b	$CDCl_3$	B	8.1–7.3 (m)[b]	8.1–7.3[b]	4.32 (2 H, q), 1.23 (3 H, t)	8.1–7.3[b]	8.1–7.3 (5 H, m)[b]
9c	$CDCl_3$	C	8.08 (1 H, d), 7.85 (1 H, d), 7.55 (1 H, t), 7.40 (1 H, t)	7.02 (d)	4.30 (2 H, q), 1.18 (3 H, t)	6.9 (br)	7.33 (5 H, s), 5.1 (2 H, AB q)
10a	DMSO	B	8.1–7.3 (m)[b]	8.1–7.3[b]	[c]	9.8 (d)	1.93 (3 H, s)
10b	DMSO	B	8.25–7.75 (2 H, m),[b] 7.75–7.35 (2 H, m)[b]	7.75–7.35[b]	[c]	10.28 (d)	8.25–7.75 (2 H, m),[b] 7.75–7.35 (2 H, m)[b]
10c	DMSO	B	8.2–7.7 (2 H, m), 7.7–6.9 (2 H, m)[b]	7.7–6.9[b]	[c]	9.5–9.1 (br d)	7.7–6.9 (5 H, m),[b] 4.95 (2 H s)
10d	DMSO	B	8.1–7.8 (2 H, m), 7.6–7.2 (2 H, m)[b]	6.8 (br d)	7.6–7.2[b]	8.1[b]	1.37 (9 H, s)

[a] A: Varian EM-360 (60 MHz). B: Varian XL-200 (200 MHz). C: Varian VXR-300 (300 MHz). [b] Overlapping signals. [c] Not observed.

Table VI. ^{13}C NMR Spectral Data[a] of Novel Benzotriazole Adducts 8–10 R^{1}CONHCH(R^2)Bt

no.	solvent	inst[b]	Bt signals	NCHN	R^2	CONH	R^1
8a	DMSO	A	145.4, 132.1, 127.4, 124.1, 119.1, 111.1	53.6	–	156.2	136.4, 128.4, 128.0, 127.4, 66.1
8b	$CDCl_3$	A	145.4, 132.8, 127.6, 124.1, 119.6, 110.1 (144.1, 126.4, 118.3)	64.8 (72.5)	36.2, 18.6, 13.2 (37.3, 18.2)	155.8	135.8, 128.4, 128.1, 127.6, 67.2
8c	DMSO	A	145.2, 132.0, 127.9, 123.9, 119.2, 111.1	72.0	31.4, 19.0, 18.1	155.7	136.4, 128.3, 127.8, 127.2, 65.9
9a	DMSO	B	145.0, 132.0, 127.8, 124.3, 119.2, 111.1	62.8	165.4, 62.5, 13.8	170.0	22.1
9b	$CDCl_3$	A	145.4, 132.1, 128.2, 124.4, 119.7, 110.3	63.5	165.4, 61.8, 13.7	167.0	132.8, 132.5, 128.6, 127.3
9c	$CDCl_3$	A	145.6, 132.8, 128.2, 124.4, 119.9, 110.9	63.9	165.0, 63.5, 13.7	155.2	135.4, 128.5, 128.3, 128.1, 67.7
10a	DMSO	A	145.1, 132.2, 127.7, 124.3, 119.2, 111.2	63.0	167.2	170.1	22.2
10b	DMSO	A	145.2, 132.5, 127.7, 124.2, 119.2, 111.5	63.9	166.8	167.1	132.3, 128.5, 127.8
10c	DMSO	A	145.2, 131.9, 127.9, 124.2, 119.2, 111.3	65.7	166.6	156.0	136.2, 128.3, 128.0, 127.6, 66.3
10d	DMSO	A	45.3, 131.8, 126.8	66.5	166.4	154.8	27.9, 79.2

[a] Bt-2-yl isomer signals in parentheses (when observed). [b] A: Varian XL-200 (50 MHz). B: Varian XL-300 (75 MHz).

ethanolic solution and can be isolated in a pure form, the analogous benzyloxycarbonyl derivative (**13c**) gives, under the same conditions, a mixture of the monomer and dimer products. Using heterogeneous conditions (i.e. in water, see the Experimental Section) monomer **13c** can be isolated in moderate yield, but attempted recrystallization from boiling EtOH leads to quantitative dimerization (see Table III, footnote *e*). Even this aqueous–heterogeneous technique yielded a monomer–dimer mixture in the case of the most reactive derivative **8e** (R^1 = BzlO, R^2 = Ph). The α-alkyl compounds (**12a–e**) are also relatively unstable and are isolated as their stable toluenesulfonate salts.

The above mentioned instability is also observed while recording the melting points of the free monoacyl aminals. Using the "flash melting point" technique (see the Experimental Section) a sharp temperature range can be determined for the melting point; however, when the samples are heated slowly a wide melting range is observed at a much higher temperature. This phenomenon is obviously due to "on-plate" dimerization.

Application of these monoacyl aminals as peptide building units depends on their reactivity in usual peptide coupling reactions. Only a few such examples have been reported;[5,6] acylations of α-amino-N-Z and α-amino-N-Boc glycine esters were accomplished by the carbodiimide method. We have now demonstrated that such monoacyl aminals, having either an unsubstituted or a carboxyl- or carboxamido-substituted central carbon atom, can be acylated by both DCC[12] and by active ester[13] coupling techniques to give the protected "*gem*-dipeptides": Fmoc-Ala-Gly(NHZ)-OH (active ester, 45 %), Z-Gly-Gly-(HNOCPh)-NH_2 (DCC, 80%), Fmoc-Gln-NH-CH_2-NHZ (active ester, 76%). The products are stable compounds; recrystallizations were performed using DMF/H_2O, AcOH/H_2O, or hot AcOH solvents without any hydrolysis or decomposition.

All new compounds prepared were characterized by their ^{1}H and ^{13}C NMR spectra, and these spectral data are recorded for the benzotriazole adducts in Tables V and VI, for the amino acid–benzotriazole adducts in Tables VII and VIII, for the monoacyl aminals in Tables IX and X, and for the *gem*-dipeptides in Tables XI and XII.

Conclusion

Mannich condensation of various amides, aldehydes, and benzotriazole gives adducts of type R^{1}CONH-CH(R^2)Bt (**8–11**), which upon reaction with NH_3 result in versatile monoacyl aminal structures (R^{1}CONH-CH(R^2)NH_2, **12–15**) in a novel, convenient route. Using protected amino acid amides as the amide component leads to "*gem*-dipeptides" (**15**). Acylation of monoacyl aminals (**12–15**) with N-protected amino acids can be accomplished by usual peptide coupling techniques, demonstrating their potential application in the synthesis of peptide analogues.

Experimental Section

Melting points were determined on a hot stage microscope and are uncorrected. "Flash melting points" were taken for the unstable compounds (see Discussion) by placing the sample on a preheated hot plate and monitoring for 1 min without further heating. Systematic repetition of the experiment at various temperatures allowed an accuracy of ±2 °C. NMR spectra were

(12) Bodanszky, M.; Klausner, Y. S.; Ondetti, M. A. *Peptide Synthesis*; Wiley: New York, 1976; p 115.
(13) Kisfaludy, L.; Schon, I. *Synthesis* **1983**, 325.

Table VII. ^{1}H NMR Spectral Data of Amino Acid–Benzotriazole Adducts 11 R^{1}CONHCH(R^2)Bt

							$R^1 = R^3CONHCH(R^4)$			
no.	solvent	instr[a]	Bt signals	NC*H*N	R^2	CONH	R^3	CONH	CH	R^4
11a	DMSO	B	8.0–7.35 (m)[b]	6.33 (t)	2.8–2.6 (1 H, m) 1.13 (3 H, d) 0.57 (3 H, d)	9.4 (d)	8.0–7.35 (5 H, m)[b]	8.65 (t)	3.9 (2 AB q)[b]	3.9 (1 H, 2 AB q)[b]
11b[c]	$CDCl_3$	C	8.15–7.9 (2 H, 2 t) 7.55–7.2 (2 H, m)[b]	6.87 (m)	2.5–2.1 (2 H, m) 1.5 (1 H, m) 1.0–0.5 (6 H, m)[b]	8.75 (d), 8.6 (d)	7.55–7.2 (5 H, m),[b] 5.1 (2 H, m)	5.93 (d)	4.3 (br t)	1.8 (1 H, m) 1.0–0.5 (6 H, m)[b]
11c[c]	DMSO	B	8.15 (2 H, m) 7.65–7.25 (2 H, m)[b]	6.4 (t)	1.4 (1 H, m) 1.3–0.4 (6 H, m)[b]	9.5 (br)	7.65–7.25 (5 H, m),[b] 5.08 (2 H, s)	7.65–7.25[b]	4.2–3.9 (m)	2.8 (1 H, br) 1.3–0.4 (8 H, m)[b]
11d[d]	$CDCl_3$	C	8.0 (1 H, d), 7.87 (1 H, d), 7.55–7.15 (2 H, m)[b]	6.7 (m)	2.2 (2 H, br) 1.25 (1 H, m) 0.8 (6 H, br s)	8.4 (br)	7.55–7.15 (5 H, m),[b] 5.03 (2 H, br)	6.3 (br)	5.47 (br)	7.55–7.15 (m)[b]
11e[d]	DMSO	C	8.1 (2 H, br) 7.7–7.0 (2 H, m)[b]	6.32 (br t)	3.15–2.6 (1 H, m)[b] 1.05 (3 H, d) 0.58 (3 H, d)	9.57 (d)	7.7–7.0 (5 H, m),[b] 4.87 (2 H, s)	7.7–7.0[b]	4.45 (br)	7.7–7.0 (5 H, m)[b] 3.15–2.6 (2 H, m)[b]
11f	$CDCl_3$ + DMSO	A	8.3–7.2 (4 H, m)[b]	8.3–7.2[b]	4.55–4.0 (2 H, m)[b] 1.17 (3 H, t)	9.6 (d)	8.3–7.2 (5 H, m)[b]	8.3–7.2[b]	4.55–4.0 (m)[b]	4.55–4.0 (1 H, m)[b]
11g	$CDCl_3$	B	8.03 (1 H, d), 7.85 (1 H, d), 7.50 (1 H, t), 7.35 (1 H, t)	7.3–7.1[b]	4.23 (2 H, q) 1.12 (3 H, t)	8.64 (d)	7.3–7.1 (5 H, br),[b] 5.06 (2 H, s)	5.87 (br t)	3.97 (br t)[b]	3.97 (1 H, br t)[b]
11h	$CDCl_3$ + DMSO	A	8.05–7.7 (2 H, m), 7.5–7.0 (2 H, br)[b]	6.85 (d)	–	9.0 (d)	7.5–7.0 (5 H, br),[b] 4.93 (2 H, s)	7.5–7.0[b]	3.72 (s)[b]	3.72[b]

[a] A: Varian EM-360 (60 MHz). B: Varian XL-200 (200 MHz). C: Varian VXR-300 (300 MHz). [b] Overlapping signals. [c] Spectrum was taken on crude diastereomeric mixtures; complex multiplicites and duplications observed. [d] Spectrum of isolated single diastereomer.

Table VIII. ^{13}C NMR Spectral Data[a] of Amino Acid–Benzotriazole Adducts 11 $R^1CONHCH(R^2)Bt$

						R^1 = $R^3CONHCH(R^4)$			
no.	solvent	instr[b]	Bt signals	NC*H*N	R^2	CONH	R^3	CONH	CH	R^4
11a	DMSO	A	144.9, 132.3, 127.2,[c] 124.0, 119.0, 111.1	68.6	31.6, 18.9, 18.2	169.6	133.9, 131.3, 128.2, 127.2[c]	166.4	42.0	–
11b[d]	$CDCl_3$	B	145.2, 132.5, 128.0, 60.5, 124.2, 119.5, 110.3 (68.5) (144.0, 126.2, 118.0)	60.5 (68.5)	41.0,24.5, 22.1, 22.0	172.0	136.0, 128.5, 128.1, 127.9, 66.5	156.2	59.5	31.5, 19.0, 17.5
11c[e]	DMSO	A	145.0, 132.0, 127.1, 123.9, 119.1, 111.2	68.9	31.2, 18.9, 18.2	172.2	137.0, 128.3, 127.6, 127.4, 65.4	156.1	58.8 [58.1]	35.9, 25.4, 14.9, 11.1 [36.2, 24.1, 14.2, 10.4]
11d[g]	$CDCl_3$	B	145.3, 132.8, 127.8, 124.4, 119.4, 110.4	60.8	42.0, 24.4, 22.1, 21.8	170.3	135.9, 128.4, 128.1, 127.8,[f] 67.0	155.3	58.2	137.9, 128.8, 127.9, 126.9[f]
11e[g]	DMSO	B	145.0, 132.4, 127.3, 124.0, 119.1, 111.2	68.6	31.8, 18.8, 18.2	172.0	136.8, 128.2, 127.6, 127.5,[f] 65.2	155.7	56.0	137.5, 129.2, 128.1, 126.4,[f] 37.8
11f	DMSO	A	145.0, 132.2, 127.9, 124.4, 119.3, 111.3	62.9[e]	165.6, 62.6,[e] 13.8	169.9	133.8, 131.4, 128.3, 127.3	166.6	42.1	–
11g	$CDCl_3$	A	145.3, 132.6, 128.0, 124.4, 119.7, 110.1 (144.2, 127.2, 118.3)	63.4 (68.5)	165.0, 61.5, 13.7	169.9	136.0, 128.4, 128.0, 127.9, 67.1	156.6	44.1	–
11h	DMSO	A	145.3, 131.9, 126.6, 123.6, 118.8, 111.9	*h*	165.7	169.7	137.0, 128.5, 127.9, 127.7, 65.6	156.6	43.5	–

[a] Bt-2-yl isomer signals in parentheses, when observed. [b] A: Varian XL-200 (50MHz). B: Varian XL-300 (75 MHz). [c] Overlapping signals. [d] Spectrum was taken on crude diastereomeric mixture. Most of the signals are duplicated, the dominant ones are listed. [e] The iLeu signals are duplicated, because of the starting iLeu was an α,β-diastereomeric mixture. [f] Interchangeable signals. [g] Spectrum of the isolated single diastereomer. In the spectrum of the crude product most of the signals are duplicated. [h] Not observed.

recorded using a Varian EM-360 (60 MHz), a Varian XL-200 (200 or 50 MHz), and a Varian VXR-300 (300 or 75 MHz) instrument as solutions in deuteriochloroform ($CDCl_3$) using TMS (δ = 0.0 ppm) for proton spectra, and the solvent signal (δ = 77.0 ppm) for carbon spectra as reference. Elemental analyses were performed in house on a Carlo Erba-1106 instrument under the supervision of Dr. D. Powell. For TLC, commercial silica gel plates (Merck DC – Alufolien Kieselgel 60F_{254}, No. 5554 with the more polar solvent systems (H, P1 and P2) or Kodak Chromagram, No. 13181 with others) were used with the following solvent systems as eluent: benzene–acetone, 2:1 (BA); benzene–methanol, 10:1 (BM); chloroform–methanol, 3:1 (CM); *n*-hexane–acetic acid–chloroform, 1:1:8 (HA); *n*-hexane–ethyl acetate–chloroform, 1:4:8 (HE); ethyl acetate–pyridine–water–acetic acid, 56:20:11:6 (P1) or 148:20:11:6 (P2). HPLC of aminal **15e** was carried out on an Altex Ultrasphere ODS column (250 × 10 mm), equilibrated with 0.1% TFA/H_2O, using a linear gradient of 5–65% CH_3CN over a period of 60 min at a flow rate of 3 mL/min. Peaks were detected at 214 nm, 0.1 AUFS.

Benzyl *N*-(1-benzotriazolyl-2-phenylethyl)carbamate (starting compound for preparation of aminal **12e**) was prepared according to the literature.[9]

Preparation of Benzyl Carbamate Adducts 8a–e (according to the procedure described in ref 9). Benzyl carbamate (3.0 g, 20 mmol), benzotriazole (2.4 g, 20 mmol), and aldehyde (20 mmol), and *p*-toluenesulfonic acid monohydrate (0.2 g, as a catalyst) in toluene (100 mL) were refluxed in a Dean–Stark apparatus for 5 h. After evaporation of the solvent the solid products were isolated with an appropriate solvent (see Table I).

Preparation of Ethyl Glyoxylate Adducts 9a–c. Benzotriazole (1.2 g, 10 mmol), ethyl glyoxylate (2.4 g, 20 mmol), and amide (10 mmol), and *p*-toluenesulfonic acid monohydrate (0.1 g, as a catalyst) in toluene (50 mL) were refluxed in a Dean–Stark apparatus for 3 h. After evaporation of the solvent the solid products were isolated by triturating the residue with a mixture of saturated aqueous $NaHCO_3$ and ether (10–10 mL).

Preparation of Glyoxylic Acid Adducts 10a–d. Amide (10 mmol), benzotriazole (10 mmol), and glyoxylic acid monohydrate (10 mmol) in benzene (30 mL) were refluxed in a Dean–Stark apparatus for (i) 4 h (**10a,b**), (ii) 2 h (**10c**), or (iii) 0.5 h (**10d**). The products, precipitating at room temperature, were filtered off and washed with ether.

Preparation of Amino Acid Amide Adducts 11a,b,d,e. Benzotriazole (1.8 g, 15 mmol), the appropriate protected amino acid amide (10 mmol) and aldehyde (15 mmol), and *p*-toluenesulfonic acid monohydrate (0.1 g, as a catalyst) in toluene (30 mL) were refluxed in a Dean–Stark apparatus for 2 h (for **11d** and **11e** after an initial stirring at room temperature for 30 min). After evaporation of the solvent (in the case of **11d** 10% solid side product was filtered off first) (i) adducts **11a** and **11e** were isolated with ethyl acetate and ether, respectively, in solid form; (ii) for adducts **11b** and **11d** the residue was extracted with ethyl acetate and 1 mol/L aqueous K_2CO_3 (10–10 mL), the organic layer was then reextracted with K_2CO_3 solution (5 mL) and water (2 × 5 mL), dried over anhydrous $MgSO_4$, and evaporated to yield the crude products as TLC pure foams. Adducts **11a,b** gave also acceptable C, H, N analyses in crude form. For **11d,e** the analytical samples were obtained by crystallization with ether (**11d**) or with ethanol (**11e**) in 30% and 62% overall yield, respectively. Evaporation of the ethereal mother liquor of **11d** gave the other diasteromer as a foam in almost pure state.

Preparation of Amino Acid Amide Adducts 11c,f. Benzotriazole (1.2 g, 10 mmol), the appropriate protected amino acid amide (10 mmol) and aldehyde (10 mmol), and *p*-toluenesulfonic acid monohydrate (0.1 g, as a catalyst) in toluene (30 mL) were stirred at room temperature for 30 min and then refluxed in a Dean–Stark apparatus for 2 h. Product **11c**, precipitating at room temperature, was filtered off and washed with ether. For **11f**, the solvent was evaporated, the residue was extracted with saturated aqueous $NaHCO_3$ and ethyl acetate (20–20 mL), the organic layer washed with water, dried ($MgSO_4$), and evaporated, and the brown, oily residue was crystallized with an ether–2-propanol, 7:1, mixture (20 mL) to give the solid product (50%). The mother liquor was evaporated and extracted with ethyl acetate and 1 mol/L K_2CO_3 solution (10–10 mL), the organic layer was washed with water, dried ($MgSO_4$), and evaporated, and the residue was

Table IX. ^{1}H NMR Spectral Data[a] of Monoacyl Aminals 12–14 $R^1CONHCH(R^3)NH_2 \cdot HX$

no.	solvent	R^1	CONH	NC*H*N	R^3	NH_2 or NH_3^+	X
12a	DMSO	7.37 (5 H, s), 5.11 (2 H, s)	8.34 (t)	4.26 (br s)[b]	4.26 (1 H, br s)[b]	8.14 (3 H, br s)	7.55 (2 H, d), 7.13 (2 H, d), 2.29 (3 H, s)
12b	DMSO	7.38 (5 H, s), 5.12 (2 H, s)	8.3 (d)	4.73 (br s)	1.65 (2 H, m), 1.3 (2 H, m), 0.85 (3 H, t)	8.15 (3 H, br s)	7.52 (2 H, d), 7.12 (2 H, d), 2.28 (3 H, s)
12c	DMSO	7.38 (5 H, s), 5.12 (2 H, s)	8.27 (d)	4.53 (br t)	2.02 (1 H, m), 0.9 (6 H, 2 d)	8.22 (3 H, br s)	7.53 (2 H, d), 7.13 (2 H, d), 2.28 (3 H, s)
12d	DMSO	7.37 (5 H, s), 5.12 (2 H, s)	8.32 (d)	4.8 (br)	1.8–1.55 (2 H, m), 1.55–1.4 (1 H, m), 0.86 (3 H, d), 0.83 (3 H, d)	8.17 (3 H, br s)	7.53 (2 H, d), 7.13 (2 H, d), 2.3 (3 H, s)
12e	DMSO	7.30–7.16 (5 H, m),[b] 4.98 (2 H, s)	7.97 (br)	5.12 (br)	7.30–7.16 (5 H, m),[b] 3.2 (2 H, m)	8.4 (3 H, br s)	7.74 (2 H, d), 7.12 (2 H, d), 2.33 (3 H, s)
13a	DMSO	1.95 (3 H, s)	9.16 (d)	5.13 (d)	8.0 (1 H, s), 7.9 (1 H, s)	8.38 (3 H, s)	7.6 (2 H, d), 7.2 (2 H, d), 2.32 (3 H, s)
13b	DMSO	8.3–8.0 (2 H, m), 7.9–7.4 (3 H, m)[b]	9.0 (d)	5.3 (d)	7.9–7.4 (2 H, m)[b]	2.7 (2 H, br)	–
13c	DMSO + $CDCl_3$	7.34 (5 H, br s),[b] 5.09 (2 H, s)	7.12 (d)	4.82 (d)	7.34 (1 H, s),[b] 7.03 (1 H, s)	2.3 (2 H, br)	–
14a	DMSO (+TFA)	7.4 (5 H, s), 5.15 (2 H, s)	8.9 (d)	5.3 (d)	11.8–10.7 (br)[c]	8.7 (3 H, br)	–

[a] Varian VXR-300 instrument (300 MHz). [b] Overlapping signals. [c] Together with trifluoroacetic acid (TFA).

Table X. ^{13}C NMR Spectral Data[a] of Monoacyl Aminals 12–14 $R^1CONHCH(R^3)NH_2 \cdot HX$

no.	solvent	R^1[b]	CONH	NC*H*N	R^3[b]	X[b]
12a	DMSO	136.4, 128.5, 128.3, 128.0, 66.2	156.1	47.1		144.9, 138.3, 128.1, 125.6, 20.8
12b	$CDCl_3$	135.9, 128.9, 128.3, 127.6, 67.0	156.1	60.7	34.2, 18.0	141.2, 140.4, 127.9, 125.9, 21.2
12c	DMSO	136.4, 128.5, 128.2, 127.9, 66.1	155.8	64.4	30.4, 18.1, 17.4	145.2, 138.0, 128.0, 125.5, 20.8
12d	DMSO	136.4, 128.4, 128.2, 127.9, 66.1	155.6	58.3	40.3, 23.7, 21.0	145.2, 138.0, 128.0, 125.5, 20.8
12e	DMSO	135.2, 128.3, 127.5, 127.2, 65.2	154.5	60.2	134.1, 126.8, 126.5, 124.7, 37.0	142.0, 138.4, 127.3, 125.9, 20.1
13a	DMSO	22.5	167.2	56.6	170.7	145.2, 138.2, 128.3, 125.7, 21.0
13b	DMSO	133.9, 131.0, 127.9, 127.1	165.9	60.7	172.9	–
13c	$CDCl_3$ (+DMSO)	135.3, 127.0, 126.5, 126.4, 64.6	154.6	60.9	171.3	–
14a	DMSO (+TFA)	137.0, 129.2, 128.9, 128.8, 67.4	156.5	59.5	168.5	–

[a] Varian VXR-300 instrument (300 MHz). [b] The close aromatic signals of R^1, R^2, and X are interchangable.

crystallized with ether to give a second fraction of the product (20%).

Preparation of Amino Acid Amide Adducts 11g and 11h. *N*-(benzyloxycarbonyl)glycine amide (1.04 g, 5 mmol), benzotriazole (0.6 g, 5 mmol), ethyl glyoxylate (1.02 g, 10 mmol) and *p*-toluenesulfonic acid monohydrate (0.05 g as catalyst) in toluene (20 mL) were refluxed for 1.5 h. For preparation of adduct **11g**, the solution was extracted with 1 mol/L K_2CO_3 (2 × 5 mL) and then with water (2 × 5 mL), treated with charcoal, and evaporated. The residue was crystallized with iPr_2O to give **11g** as a white solid. For preparation of adduct **11h**, the solvent was evaporated, the residue was shaken with 1 mol/L NaOH and ether (20–20 mL) for 10 min, and the aqueous solution was acidified with AcOH to give **11h** as an off-white solid.

Preparation of Monoacyl Aminals 12a–e. Adduct 8 (10 mmol) and finely powdered K_2CO_3 (3.0 g) were stirred in methanolic NH_3 solution (30 mL, saturated at 0 °C) at 25 °C, in a closed flask (under pressure) for 3 h. The solid was filtered off, and the filtrate was evaporated in vacuo, at 25 °C, to dryness. The residue was stirred with dry ether for 30 min, and the solid was filtered off. *p*-Toluenesulfonic acid solution (10 mmol in 30 mL ethyl acetate) was added to the ethereal solution. The precipitating salt was crystallized at 5 °C overnight and then filtered off and washed with cold ethyl acetate.

Preparation of 1-(Acetylamino)-1-aminoacetamide (13a). Adduct **9a** (2.0 g, 7.6 mmol) was stirred in methanolic NH_3 solution (10 mL, saturated at 0 °C) at 25 °C, in a closed flask (under pressure) for 5 days. The solvent was evaporated, and the residue crystallized with ether to yield a pink solid (1.0 g, 100%). Stirring the solid with MeOH gave white, analytically pure product (0.91 g, 91%), mp 130–132 °C.

Preparation of 1-Amino-1-(benzoylamino)acetamide (13b). Adduct **9b** (0.5 g, 1.5 mmol) was dissolved in ethanolic NH_3 solution (10 mL, saturated at 0 °C) and was kept at 5 °C in a closed flask overnight. After evaporation of the solvent (in vacuo, at 25 °C) the product was isolated with ether in a pure state (0.3 g, 86%), mp 174–182 °C.

Preparation of 1-Amino-1-((benzyloxycarbonyl)amino)-acetamide (13c). Adduct **9c** (2.0 g, 5.9 mmol) was stirred with commercial concentrated NH_4OH solution (20 mL) at 25 °C for 2 h. After addition of water (20 mL) the precipitate was filtered off and washed with cold water to give a white, solid product (0.48 g, 37%). Recrystallization by dissolving at room temperature in a $CHCl_3$–MeOH, 1:1, mixture (2 mL), and precipitation with hexane (5 mL) gave the analytical sample, mp 113 °C. Attempted recrystallization from boiling EtOH led to quantitative dimerization to α,α'-aminobis(((α-benzyloxycarbonyl)amino)acetamide) $[ZNHCH(CONH_2)]_2NH$: mp 177–180 °C; ^{1}H NMR (DMSO-d_6) δ 3.4 (3 H, b s, CONH + NH), 4.7 (2 H, t, CH), 5.0 (4 H, s, Z-CH_2), 7.7–7.1 (14 H, b, Ar + $CONH_2$); ^{13}C NMR (DMSO-d_6) δ 171.3 ($CONH_2$), 156.0 (Z-CO), 136.9, 128.3, 127.7 (Ar), 65.6 (Z-CH_2), 64.0 (CH). Anal. Found C, 55.9; H, 5.4; N, 16.3. $C_{20}H_{23}N_5O_6$ requires; C, 56.2; H, 5.4; N, 16.5.

Preparation of 1-Amino-1-((benzyloxycarbonyl)amino)-acetic Acid (14a). Adduct **10c** (5 g, 15.3 mmol) was dissolved in methanolic NH_3 solution (50 mL, saturated at 0 °C) and stirred at 25 °C in a closed flask (under pressure) for 24 h. After evaporation of the solvent (in vacuo, at 25 °C) the product was isolated with acetone in a pure state (2.4 g, 70%), mp 142–144 °C (lit.[6] mp 135 °C).

Preparation of "*gem*-Dipeptides" 15a-e. Adducts **11a-e** (0.5 g) and finely powdered anhydrous K_2CO_3 (0.5 g) were stirred in methanolic NH_3 solution (5 mL, saturated at 0 °C) at room temperature in a closed flask (under pressure) for 4 h. The solvent was evaporated, and ice water (5 mL) was added to the residue. Product **15c** solidified and was filtered off, while the others formed oils which were extracted with ethyl acetate (2 × 10 mL). The organic solutions were then washed with 1 mol/L K_2CO_3 solution (5 mL) and saturated NaCl solution (2 × 5 mL), dried over anhydrous $MgSO_4$, and evaporated to give the crude products. The products were pure by TLC and gave clean NMR spectra but duplicated ^{13}C signals for the diastereomeric mixtures **15b–e**. Analytical samples of **15b** and **15e** were obtained with ether (free bases), while the others were converted to tosylate salts with equimolar toluenesulfonic acid solution (0.5 M in ethyl acetate); for **15b** a 4× volume of ether was used to precipitate the salt.

Preparation of "*gem*-Dipeptides" 15f–h. Adducts **11f–h** (0.5 g) were stirred in methanolic NH_3 solutions (5 mL, saturated at 0 °C) at room temperature in closed flasks (under pressure) for (i) 4 days for **15f**, (ii) 12 h for **15g**, or (iii) 7 days for **15h**. After

Table XI. ^{1}H NMR Spectral Data[a] of "*gem*-Dipeptides" 15 $R^1CONHCH(R^3)NH_2 \cdot HX$

		$R^1 = R^4CONHCH(R^5)$								
no.	solvent	R^4	CONH	CH	R^5	(R^1) CONH	NC*H*N	R^3	NH_2 or NH_3^+	X
15a	DMSO	7.9 (2 H, d), 7.5 (3 H, m)[b]	8.82 (t)	4.0 (br s)[b]	4.0 (1 H, br s)[b]	8.75 (d)	4.72 (br)	2.03 (1 H, m), 0.95 (6 H, m)	8.2 (br s)	7.50 (2 H, m),[b] 7.13 (2 H, d), 2.28 (3 H, s)
15b	$CDCl_3$	7.36 (5 H, s), 5.11 (2 H, s)	5.57 (d)	3.9 (t)	2.1 (1 H, m), 1.0–0.85 (6 H, m)	6.37 (br d)	4.8 (q)	1.67 (1 H, m), 1.40 (2 H, br t), 1.0–0.85 (6 H, m)[b]	1.87 (br s)	–
15c	$CDCl_3$	7.36 (5 H, s), 5.1 (2 H, s)	5.74 (d)	4.0 (t)	1.9–1.6 (2 H, m),[b] 1.2–1.05 (1 H, m),[c] 1.0–0.85 (6 H, m)[b]	6.58 (d)	4.58 (t)	1.6–1.45 (1 H, m),[c] 1.0–0.85 (6 H, m)[b]	1.9–1.6 (m)[b]	–
15d	DMSO	7.5–7.2 (5 H, m),[b] 5.08 (2 H, s)	9.08 (d)[c]	5.36 (d)	7.5–7.2 (5 H, m)[b]	8.12 (d)[c]	4.83 (br)	1.75–1.15 (3 H, m), 0.83 (3 H, d), 0.56 (3 H, d)	8.2 (br s)	7.55 (2 H, d), 7.12 (2 H, d), 2.28 (3 H, s)
15e	$CDCl_3$	7.45–7.10 (5 H, m),[b] 5.07 (2 H, s)	5.8 (br t)	4.6–4.3 (m)[b]	7.45–7.10 (5 H, m),[c] 3.04 (2 H, br d)	6.5 and 6.2 (2 br)	4.6–4.3 (m)[c]	1.7–1.5 (1 H, m), 0.9–0.65 (6 H, m)	1.9 (br s)	–
15f	DMSO	7.9 (2 H, d), 7.48 (3 H, br)[b]	8.8 (br s)[c]	3.95 (s)[b]	3.95 (1 H, s)[b]	8.28 (br s)[c]	4.93 (s)	7.48 (1 H, br),[b] 7.25 (1 H, s)	2.2 (2 H, br)	–
15g	DMSO	7.35 (5 H, br s),[b] 5.05 (2 H, s)	8.2 (br s)	3.65 (s)[b]	3.65 (1 H, s)[b]	7.35 (br s)[b]	4.9 (s)	7.35 (br s)[b]	3.2–2.7 (br)	–
15h	D_2O[d]	7.53 (5 H, s), 5.24 (2 H, s)	*e*	5.24 (s)[b]	5.24 (1 H, s)[b]	*e*	*e*	*e*	*e*	–

[a] Spectral data given for purified (in the case of **15b–e** diastereohomogeneous) products, taken on Varian VXR-300 (300 MHz) (for **15e** on Varian XL-200 (200 MHz)) instrument. [b] Overlapping signals. [c] Interchangable signals. [d] With 1 equiv of K_2CO_3. [e] Overlapping with the H_2O signal (3.95 ppm).

Table XII. ^{1}H NMR Spectral Data[a] of *gem*-Dipeptides 15 $R^1CONHCH(R^3)NH_2 \cdot HX$

		$R^1 = R^4CONHCH(R^5)$				(R^1)			
no.	solvent	R^4[c]	CONH	CH	R^5[c]	CONH	NC*H*N	R^3	X
15a	DMSO	133.9, 131.4, 128.3, 127.3	170.1	42.4	–	166.6	61.6	30.3, 18.1, 17.2	145.2, 138.0, 128.2, 125.5, 20.8
15b	$CDCl_3$	136.2, 128.5, 128.2, 128.0, 67.0	156.5	58.3	30.9, 19.2, 17.9	171.2	60.7	45.3, 24.9, 22.5, 22.3	–
15c[c]	$CDCl_3$	136.2, 128.5, 128.1, 66.9	156.4	59.9	37.3, 24.7, 15.5, 11.3	171.3	64.1	32.9, 18.0, 17.9	–
15d	DMSO	136.9, 128.4,[d] 128.1, 127.8, 65.7	155.8	58.2	137.4, 128.4,[d] 128.2, 127.9	170.9	55.7	40.2, 23.5, 22.9	145.1, 138.1, 127.7, 125.6, 20.9
15e[d]	$CDCl_3$	136.4, 128.4, 128.1, 127.9, 66.9	156.0	56.5	136.2, 129.3, 128.6, 127.0, 38.8	170.9	64.0	32.7, 17.6	–
15f	DMSO	134.0, 131.4, 128.4, 127.4	169.0	42.8	–	166.6	60.2	172.6	–
15g	DMSO	137.1, 128.4, 127.9, 127.7, 65.5	156.6	43.6	–	169.1	60.1	172.5	–
15h	D_2O[e]	137.7, 130.3, 129.9, 129.3, 68.5	159.6	45.1	–	172.7	62.6	177.2[f]	–

[a] Spectral data given for purified (in the case of **15b–e** diastereohomogeneous) products, taken on Varian VXR-300 (300 MHz) (for **15e** Varian XL-200 (200 MHz)) instrument. [b] The close aromatic signals are interchangable. [c] Small (10–15% intensity) additional iLeu peaks observed, due to the other α,β-diastereomer present: 58.8, 37.4, 26.2, 14.3, 11.6. [d] Overlapping signals. [e] With 1 equiv, K_2CO_3. [f] COO^-.

evaporation of the solvent, products **15f** and **15g** were isolated with ether. The obtained sodium salt of **15g** was dissolved in acetone decolorified with charcoal and precipitated by acidification with acetic acid. The crude products were pure by TLC and gave clean NMR spectra; for crude **15f** good C, H, N analyses were also obtained. An analytial sample of **15g** was obtained by washing with MeOH; **15h** was purified by dissolving in 1 mol/L K_2CO_3 solution and reprecipitating, after filtration, with acetic acid.

Preparation of 1-(*N*-Fluorenylmethyloxycarbonyl-L-alanylamino)-1-((benzyloxycarbonyl)amino)acetic Acid (Fmoc-Ala-Gly(NHZ)-OH). 1-Amino-1-((benzyloxycarbonyl)-amino)acetic acid (**14a**, 0.22 g, 1 mmol), *N*-fluorenylmethyloxycarbonyl-L-alanine pentafluorophenyl ester (Fmoc-Ala-OPfp, purchased from BioSearch Co., 0.48 g, 1 mmol), and triethylamine (0.2 mL, 1.4 mmol) were stirred in chloroform (10 mL) overnight. After addition of 1 mol/L HCl(aq) (5 mL) the precipitate was filtered off and washed with water and ether to give the crude product (0.23 g, 45%), mp 205–210 °C. Recrystallization from DMF–water gave the analytical sample, mp 205–207 °C; ^{1}H NMR (DMSO-d^6) δ 1.5 (3 H, m, Me), 4.25–4.5 (4 H, m, fluorenyl-CH and CH_2, Ala-CH), 5.12 (2 H, s, Z-CH_2), 5.6 (1 H, m, NCHN), 7.2–7.4 (9 H, m, arom), 7.64 (2 H, t, fluorenyl), 7.8 (2 H, d, fluorenyl), 7.55 (1 H, d, NH), 8.02 (1 H, 2 d, NH), 8.44 (1 H, 2 d, NH); ^{13}C NMR (DMSO-d_6) δ 172.6 (COOH), 169.8 (amide-CO), 155.8 and 155.5 (carbamate-CO signals), 144.0, 143.8, 140.7, 128.4, 125.3, 120.1 (fluorenyl), 136.7, 127.8, 127.7, 125.3 (Ph), 65.8 and 65.7 (2 CH_2), 57.6 (NCN), 49.8 (Ala-CH), 46.7 (fluorenyl-CH), 18.1 (CH_3). Anal. Found: C, 64.0; H, 5.,4; N, 8.1. $C_{28}H_{27}N_3O_7$ requires: C, 65.0; H, 5.3; N, 8.1.

Preparation of 1-[*N*-(Benzyloxycarbonyl)glycylamino]-1-(benzoylamino)acetamide (Z-Gly-Gly-(HNOCPh)-NH_2). 1-Amino-1-(benzoylamino)acetamide (**13b**, 0.45 g, 2 mmol), *N*-(benzyloxycarbonyl)glycine (Z-Gly, 0.45 g, 2.1 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (DCC, 0.45 g, 2.2 mmol) were stirred in dry tetrahydrofuran at 25 °C overnight. The resulting gel was suspended with ethyl acetate and centrifuged twice. The solid residue was suspended in dimethylformamide (15 mL), and the insoluble dicyclohexylurea (DCU) was filtered off. Addition of ether (70 mL) to the filtrate resulted in precipitation of the crude product. Stirring with a chloroform–methanol, 1:1, mixture (10 mL) gave a TLC- and NMR-pure white powder (0.34 g, 80%, R_f = 0.7/P1). An analytical sample was obtained by recrystallization from acetic acid–water: mp 209–211 °C; ^{1}H NMR (DMSO-d_6) δ 2.6–2.9 (2 H, m, Gly-CH_2), 5.05 (2 H, s, Z-CH_2), 5.91 (1 H, t, NCHN), 7.2–7.65 (11 H, m, 8 H, arom + Z-NH + NH_2), 7.9 (2 H, d, Ph), 8.37 (1 H, d, Gly-NH), 9.02 (1 H, d, PhCO*NH*); ^{13}C NMR (DMSO-d_6) δ 169.8 and 169.2 ($CONH_2$ and Gly-CONH), 166.1 (PhCONH), 156.6 (Z-CO), 137.0, 128.4, 127.7 (Z-Ph), 133.5, 131.7, 128.3, 127.5 (*Ph*CO), 65.6 (Z-CH_2), 57.1 (N-C-N), 43.6 (Gly-CH_2). Anal. Found; C, 59.2; H, 5.2; N, 14.5. $C_{19}H_{20}N_4O_5$ requires: C, 59.4; H, 5.2; N, 14.6.

Preparation of 1-(*N*-Fluorenylmethyloxycarbonyl-L-glutamylamino)-1-((benzyloxycarbonyl)amino)methane (Fmoc-Gln-NH-CH_2-NHZ). *N*-Fluorenylmethyloxycarbonyl-L-glutamine pentafluorophenyl ester (Fmoc-Gln-OPfp, purchased from BioSearch Co., 0.53 g, 1 mmol), benzyl(aminomethyl)carbamate *p*-toluenesulfonate (**12a**, 0.35 g, 1 mmol), and triethylamine (0.28 mL, 2 mmol) were stirred in dry dimethylformamide (10 mL) at 25 °C overnight. The resulting precipitate was filtered off and washed successively with dimethylformamide (5 mL) and ethanol (5 mL) to yield the crude, NMR-pure product as a white powder (0.4 g, 76%). An analytical sample was obtained by recrystallization from AcOH: mp 183–185 °C; ^{1}H NMR (DMSO-d^6) δ 1.6–2.0 (2 H, m, Gln-βCH_2), 2.0–2.25 (2 H, b, Gln-γCH_2), 4.0 (1 H, m, Gln-CH), 4.25 (3 H, b s, Fmol-CH + CH_2), 4.4 (2 H, b, NCH_2N), 5.04 (2 H, s, Z-CH_2), 6.8 (1 H, b s, NH), 7.25–8.0 (14 H, m, arom + NH); ^{13}C NMR (DMSO-d_6) δ 173.7 ($CONH_2$), 171.9 (amide-CO), 156.1 and 155.9 (carbamate-CO signals) 143.9, 140.7, 127.8, 127.1, 125.3, 120.1 (fluorenyl), 137.0, 128.3, 127.6 (Ph), 65.7 and 65.4 (carbamate-CH_2 signals), 54.3 (Gln-CH), 46.6 (fluorenyl-CH), 45.6 (NCH_2N), 31.6 (Gln-γCH_2), 27.8 (Gln-βCH_2). Anal. Found: C, 64.8; H, 5.7; N, 10.5. $C_{29}H_{30}N_4O_6$ requires: C, 65.65; H, 5.7; N, 10.6.

Registry No. **5** (R^1 = OBzl), 621-84-1; **5** (R^1 = Me), 60-35-5; **5** (R^1 = Ph), 55-21-0; **5** (R^1 = OBu-*t*), 4248-19-5; **5** (R^1CO = Bz-Gly), 5813-81-0; **5** (R^1CO = Z-Val), 13139-28-1; **5** (R^1CO = Z-DL-Ile), 125515-94-8; **5** (R^1CO = Z-DL-alloIle), 33878-58-9; **5** (R^1CO = Z-DL-Phg), 125515-95-9; **5** (R^1CO = Z-DL-Phe), 17324-88-8; **5** (R^1CO = Z-Gly), 949-90-6; **6** (R^2 = H), 50-00-0; **6** (R^2 = Pr), 123-72-8; **6** (R^2 = *i*-Pr), 78-84-2; **6** (R^2 = *i*-Bu), 590-86-3; **6** (R^2 = Ph), 100-52-7; **6** (R^2 = COOEt), 924-44-7; **7**, 95-14-7; **8a**, 125453-11-4; **8b**, 125453-12-5; **8c**, 125453-13-6; **8d**, 125453-14-7; **8e**, 125453-15-8; **9a**, 124676-18-2; **9b**, 124676-16-0; **9c**, 124676-15-9; **10a**, 125453-16-9; **10b**, 125453-17-0; **10c**, 124676-19-3; **10d**, 125453-18-1; **11a**, 125453-19-2; (*R*)-(*R**,*S**)-**11b**, 125453-20-5; (*S*)-(*R**,*R**)-**11b**, 125453-21-6; **11c**, 125453-22-7; (*R**,*R**)-(±)-**11d**, 125453-23-8; (*R**,*S**)-(±)-**11d**, 125453-24-9; (*R**,*R**)-(±)-**11e**, 125453-25-0; (*R**,*S**)-(±)-**11e**, 125453-26-1; **11f**, 125453-27-2; **11g**, 125453-28-3; **11h**, 125453-29-4; **12a**, 125453-30-7; **12b**, 125453-31-8; **12c**, 125453-32-9; **12d**, 125453-33-0; **12e**, 125453-34-1; **13a**, 125453-35-2; **13b**, 124676-21-7; **13c**, 124676-20-6; **14a**, 124676-23-9; **15a**, 125453-36-3; L-(*R*)-**15b**, 125453-37-4; L-(*S*)-**15b**, 125453-38-5; **15c**, 125453-39-6; (*R**,*R**)-(±)-**15d**, 125453-40-9; (*R**,*S**)-(±)-**15d**, 125453-41-0; **15e**, 125453-42-1; **15f**, 125453-43-2; **15g**, 125453-44-3; **15h**, 125453-45-4; Fmoc-Ala-OPfp, 86060-86-8; Fmoc-Ala-Gly-(NHZ)-OH, 124676-24-0; Z-Gly-OH, 1138-80-3; Z-Gly-Gly-(NHCOPh)-NH_2, 125453-46-5; Fmoc-Gln-OPfp, 86061-00-9; Fmoc-Gln-$NHCH_2$nHz, 125453-47-6; OHCCOH, 298-12-4; $[ZNHCH(CONH_2)]_2NH$, 124676-26-2.