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Toward Synthesis of α-Alkyl Amino Glycines (A3G), New Amino Acid Surrogates

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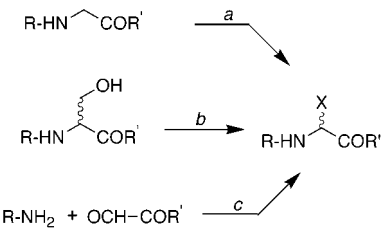
Abstract: A general method giving access to protected α-alkyl amino glycines (A3G) **4** from the previously described precursor α-isopropylthioglycine **1** is described. In the presence of *N*-bromosuccinimide, displacement of the thiol by a large variety of amines afforded the corresponding racemic amino acid mimics. The efficiency of the reaction was strongly dependent on the protective groups of the nucleophile used in the condensation.

Nonnatural amino acids and amino acid mimics have become increasingly important in the discovery of pharmacologically active peptides and peptidomimetics. In this respect, a large variety of strategies for the synthesis of new amino acid isosteres has appeared with the coming of age of combinatorial chemistry.[1] An interesting approach is the synthesis of α-substituted glycines in which the Cα-substituent is replaced by a heteroatom, leading to a variety of side chains and thereby increasing the molecular diversity of these amino acid analogues.

Three different strategies have been developed for the preparation of α-heterosubstituted glycines. The first synthetic route (Scheme 1, route *a*) relies on the functionalization of a protected glycine that can occur through halooxazolone formation[2] or by radical bromination,[3−5] followed in both cases by nucleophilic halogen displacement. A second alternative (Scheme 1, route *b*) involves oxidative cleavage of serine- and threonine-containing peptides, which directly affords acetoxyglycine-containing molecules.[6] The third synthetic route relies on the condensation of an amide or carbamate (Scheme 1, route *c*, R= R″CO, R″OCO) with glyoxylic acid to give the corresponding N-acylated α-hydroxyglycine. Following the initial reports by Ben-Ishai[7] and Schouteeten[8] the synthetic possibilities of this reaction have been largely

SCHEME 1



investigated. For instance, replacement of the α hydroxyl function (Scheme 1, X = OH) by an alkoxy (X = OR) or alkylthio (X = SR) group could be performed under acidic conditions.[7,9,10] Access to α-aminoglycine (Scheme 1, $X = NH_2$) was then accomplished by displacement of the alkylthio group by alkylamines with the help of mercuric salts.[9,11] Reduction of α-azidoglycine[12] directly accessible from the hydroxyl function using diphenylphosphoryl azide also leads to α-aminoglycine. Alternatively, α-hydroxyglycine could be converted into the corresponding acetate, which was displaced by nucleophiles such as thiols[13] or amines.[14] An interesting application is the addition of enantiopure α-amino acid esters to α-haloglycine-containing peptides, which yields the corresponding modified oligopeptides with remarkable stereoselectivity.[16] Further improvement in the access to α-heterosubstituted glycines was obtained by way of a three-component reaction using amide (or carbamate) and glyoxylic acid in the presence of benzotriazole or propane-2 thiol to give α-benzotriazolyl- or α-isopropylthioglycine. The benzotriazolyl or isopropylthio accessory group can then be directly displaced by ammonia[15] or carbamates[17] to afford α-amino or α-acylamino glycines, respectively.

As a result of the presence of a geminal diamine function, the stability of α-alkylamino glycines **4** (Scheme 2) is generally restricted to very particular cases. It has been previously demonstrated that acylation of only one of the nitrogens (R_1, R_3, or R_4) allows isolation of the corresponding compound.[9,15] We previously reported that incorporation of α-aminoglycine within a peptide sequence could be automated[17] using the fully protected Boc, Fmoc amino glycine **4** (R_1 = Boc, R_3 = Fmoc, R_2 = R_4 = H) as the smallest of the protected basic amino acids. This unique compound, which allowed interesting applications after incorporation into peptide sequences and further acylation,[18−20] has also been obtained as a

[†] To whom this work is dedicated.

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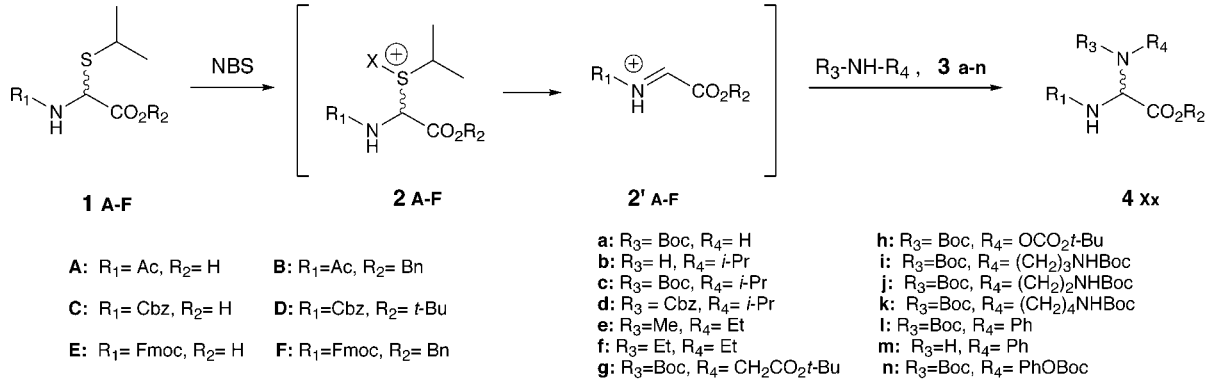
SCHEME 2



single enantiomer by total synthesis from *S*-Cbz-serine or by papain resolution of the corresponding ester or amide.[21] Access to α-amino glycine derivatives is therefore restricted to compounds bearing acylamino side chains with the exception of a methyl amino group. We therefore believe that the problem of a general access to A3G remains unsolved.

The strategy followed is shown in Scheme 2. The numbering used throughout this study refers to the four structures **1**−**4** of Scheme 2. The final compound **4Xx** was identified by two additional letters (**Xx**), a capital letter referring to the substituents of the electrophilic precursor (**1X**) and the lower case letter referring to the substituents brought by the nucleophile **3x**. The three-component condensation of amide/carbamate R_1NH_2, isopropyl mercaptan, and glyoxylic acid (R_2 = H) according to reference[22] gave the protected α-isopropylthio glycine derivatives **1A**, **1C**, and **1E** in good to excellent yields. The corresponding esters could be obtained under similar conditions starting from the corresponding benzyl or *tert*-butyl glyoxylate. It was found, however, that the esters **1B**, **1D**, and **1F** could be obtained more efficiently by esterification of the acidic precursors with the desired alcohol, conditions that we systematically used as described in the experimental protocol. Displacement of sulfur in **1** by amines, amides, or carbamates occurred under very mild conditions (THF, 0 °C) in the presence of *N*-bromosuccinimide. It was observed that condensation of stoichiometric amounts of **1** and **3** requires only 0.5 equiv of NBS. This suggests that NBS first generates the bromosulfonium salt **2** (X = Br), which decomposes into **2′** with the simultaneous formation of isopropyl sulfenyl bromide (*i*-PrSBr). The latter acts as a sulfenylating agent on **1** to give **2** (X = *i*-PrS), which decomposes to the same iminium **2′** with simultaneous formation of di-isopropyl disulfide. The presence of this disulfide was indeed detected by comparison with an authentic sample and was quantified to 100% by analytical HPLC, thereby validating the proposed mechanism for the reaction of **1** with NBS.

The intermediate **2** (or more likely **2′** whose lowest unoccupied molecular orbital is 0.8 eV lower) further reacts with the incoming nucleophile **3**, which provides the side chain of the amino acid equivalent. The one-pot conversion **1** → **4** occurred smoothly over a few hours, and the resulting adduct **4** was purified by silica gel chromatography in order to remove (i) the di-isopropyl disulfide, (ii) the starting carbamate R_1NH_2 and glyoxylate resulting from retrocondensation of iminium **2′** and, (iii) the α-hydroxy glycine resulting from hydration of the latter.

The irreversibility of the condensation affording **4Xx** was demonstrated in a particular case. Thus, the composition of a mixture of **4Ec** and 0.5 equiv of anhydrous HBr in THF at room temperature (i.e., under conditions similar to the synthetic procedure) was followed by reverse-phase chromatography over a period of 18 h; under these conditions no decomposition of the compound was observed as judged from the integration of the corresponding **4Ec** HPLC peak.

As demonstrated by the selected examples listed in Table 1, the reaction allowed access to amino acid analogues containing alkyl (entries 2 and 3), hydroxyalkyl (entry 5), alkylcarboxylates (entry 4), alkylamino (entry 6), and aryl (entries 7 and 8) side chains. Within these series virtually any analogue can be obtained. Interestingly, the corresponding homologues, i.e., with a shorter or a longer side chain, are easily accessible (entries 3 and 6). Proline analogues have been previously obtained directly from glyoxylic acid and the suitably protected ethylenediamine.[23] Access to histidine and tryptophan analogues have not been possible because of instability of the corresponding 4-aminoimidazole and 3-aminoindole. The yields are generally less affected by the nature of the protecting groups of **1** (compare entries 2, 4, and 7) than by the nature of the nucleophile **3**. For instance, the rather constrained analogue **4Eg** (entry 4) was isolated with 60% yield, whereas the phenylalanine mimic **4El** (entry 7) was obtained with 15% yield. None of the acetylated analogues **4Al**, **4Bl**, **4Am**, or **4Bm** could be isolated following the procedure depicted in Scheme 2. The synthesis of compound **4Am** was performed as described in Scheme 3. Condensation of acetamide and benzyl glyoxylate under the conditions described by Schouteeten et al.[8] afforded the corresponding α-hydroxy-

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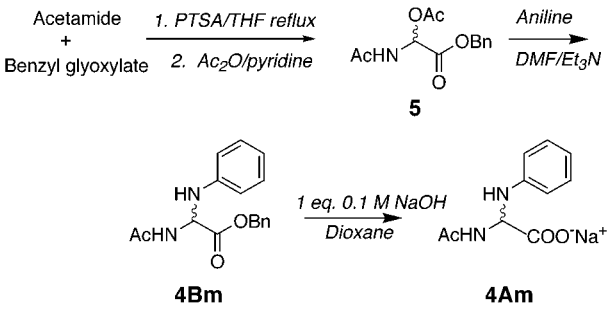
TABLE 1. Chemical Yields of Isolated A3G (see also Scheme 2)

entry	mimic of	R_1	R_2	R_3	R_4	yield, %
1	alanine					
	4Ea[22]	Fmoc	H	Boc	H	82
2	leucine					
	4Cc	Cbz	H	Boc	*i*-Pr	48
	4Dc	Cbz	*t*-Bu	Boc	*i*-Pr	45
	4Db	Cbz	*t*-Bu	H	*i*-Pr	80
	4Ec	Fmoc	H	Boc	*i*-Pr	45
	4Fc	Fmoc	Bn	Boc	*i*-Pr	44
	4Ed	Fmoc	H	Cbz	*i*-Pr	20
3	isoleucine					
	4Be	Ac	Bn	Me	Et	74
	4Bf[a]	Ac	Bn	Et	Et	89
4	glutamate					
	4Eg	Fmoc	H	Boc	$CH_2CO_{2-t}Bu$	61
	4Cg	Cbz	H	Boc	$CH_2CO_{2-t}Bu$	53
5	serine					
	4Eh	Fmoc	H	Boc	OBoc	60
6	lysine					
	4Ei	Fmoc	H	Boc	$(CH_2)_3NHBoc$	37
	4Ci	Cbz	H	Boc	$(CH_2)_3NHBoc$	40
	4Ej[a]	Fmoc	H	Boc	$(CH_2)_2NHBoc$	40
	4Ek[a]	Fmoc	H	Boc	$(CH_2)_4NHBoc$	30
7	phenylalanine					
	4El	Fmoc	H	Boc	Ph	15
	4Bm[b]	Ac	Bn	H	Ph	20
	4Am[b]	Ac	H	H	Ph	20
8	tyrosine					
	4En	Fmoc	H	Boc	PhOBoc	22
	4Cn	Cbz	H	≪	PhOBoc	12

[a] Homologous to the amino acid. [b] Derivative obtained according to Scheme 3.

SCHEME 3



glycine isolated as a solid in 30% yield. Displacement of its acetyl derivative **5** with aniline occurred in almost quantitative yield to provide **4Bm,** which was saponified with a stoichiometric amount of sodium hydroxide in dioxane to give **4Am**.

In summary, this report describes the first general access to racemic, orthogonally protected α-alkylamino glycines, which are new interesting building blocks for the synthesis of peptidomimetics. The synthesis of such A3G-containing peptide mimics is currently under investigation.

Experimental Section

General Methods. All solvents used were purified according to standard procedures. NBS was crystallized from acetic acid, dried in vacuo, and stored under vacuum over P_2O_5. Flash chromatography was performed using silica (60 A C.C 35−70 μm). Boc-protected amines were visualized with ninhydrin and sulfur-containing compounds with aniline followed by bromine treatment. ^1H and ^{13}C NMR were recorded at 200, 250, or 300 MHz, and the chemical shifts are reported with respect to the residual solvent used. Melting points were determined using a capillary apparatus. Low-resolution mass spectra were acquired in ESI, FAB or IC modes whereas high-resolution spectra were acquired in ESI or IC.

Synthesis of Protected α-Isopropylthioglycine Derivatives 1. 2-Acetamido 2-Isopropylthio Acetic Acid, Ac-Gly-(S-*i*Pr)-OH (1A). Acetamide (30 g, 0.5 mol), isopropanethiol (100 mL, 1.07 mol), 50% aqueous glyoxylic acid (75 mL, 0.6 mol), and *p*-toluenesulfonic acid (PTSA, 0.7 g) were stirred in toluene (500 mL) under reflux in a Dean−Stark apparatus until no water was extracted. Crystallization from heptane/ethyl acetate gave **1A** (78.0 g, 81%), mp 135 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 1.33 (d, J = 6.6 Hz, 3H), 1.35 (d, J = 6.6 Hz, 3H), 1.99 (s, 3H), 3.2 (h, J = 6.6 Hz, 1H), 5.45 (d, J = 8.8 Hz, 1H), 8.75 (d, J = 8.8 Hz, 1H), 12.9 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.72, 23.58, 24.10, 35.31, 53.24, 169.48, 170.74. MS (IC, isobutane): m/z 192 $[M + H]^+$. Anal. Calcd for $C_7H_{13}NO_3S$: C, 43.96; H, 6.85; N, 7.32. Found: C, 43.81; H, 6.83; N, 7.37.

2-Acetamido 2-Isopropylthio Acetic Acid Benzyl Ester, Ac-Gly(S-*i*Pr)-OBn (1B). To **1A** (38.24 g, 0.2 mol), benzyl alcohol (23.71 g, 0.22 mol), and DMAP (1.00 g, 0.008 mol) in THF (400 mL) at 0 °C was added DCC (45.38 g, 0.22 mol). DCU was removed by filtration after 12 h, and the solvent was removed under vacuum. Flash chromatography (heptane/EtOAc, 1/1) gave **1B** (31.5 g, 56%), mp 40 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 1.26 (d, J = 6.6 Hz, 3H), 1.29 (d, J = 6.6 Hz, 3H), 1.99 (s, 3H), 3.19 (h, J = 6.6 Hz, 1H), 5.29 (s, 2H), 5.58 (d, J = 7.9 Hz, 1H), 7.47 (bs, 5H), 8.95 (bd, J = 7.9 Hz, 1H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 22.88, 23.78, 24.24, 35.83, 53.40, 67.24, 128.56, 128.78, 128.86, 136.29; 169.56, 169.89. MS (ESI): m/z 304 $[M + Na]^+$. HRMS (IC, isobutane): calc for $C_{14}H_{20}NO_3S$ $[M + H]^+$ 282.1163, obsd 282.1159.

2-[*N*-Benzyloxycarbonyl]amino 2-Isopropylthio Acetic Acid, Cbz-Gly(S-*i*Pr)-OH (1C). Benzylcarbamate (7.5 g, 0.05 mol), isopropanethiol (10 mL, 0.107 mol), 50% aqueous glyoxylic acid (7.5 mL, 0.06 mol), and PTSA (0.15 g) in toluene (50 mL) were stirred under reflux in a Dean−Stark apparatus until no water was extracted. The toluene was removed under vacuum, and the residue was crystallized in heptane/EtOAc to afford **1C** (13 g, 90%), mp 83 °C (lit.[8] 82−84 °C). Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94. Found: C, 54.92; H, 5.91; N, 4.87.

2-[*N*-Benzyloxycarbonyl]amino 2-Isopropylthio Acetic Acid *tert*-Butyl Ester, Cbz-Gly(S-*i*Pr)-O*t*Bu (1D). To **1C** (10.00 g, 0.035 mol) dissolved in THF (100 mL) containing *tert*-butanol (3.68 mL, 0.039mol) was added DCC (8.01 g, 0.039 mol) at 0 °C. After 12 h DCU was removed by filtration. Flash chromatography of the oily residue (heptane/EtOAc, 8/2) gave **1D** (4.46 g 37%). ^1H NMR (250 MHz, $CDCl_3$): δ 1.33 (d, J = 7.2 Hz, 3H), 1.35 (d, J = 7.2 Hz, 3H), 1.49 (s, 9H), 3.22 (hept, J = 7.2 Hz, 1H), 5.08 (d, J = 12.0 Hz, 1H), 5.20 (d, J = 12 Hz, 1H), 5.23 (d, J = 8.5 Hz, 1H), 6.05 (d, J = 8.5 Hz, 1H), 7.36 (bs, 5H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 23.43, 24.10, 27.86, 36.13, 56.10, 67.22, 82.99, 128.17, 128.53, 136.06, 154.80, 168.35. MS (ESI): m/z 339.8 $[M + H]^+$, 361.8 $[M + Na]^+$, 701.0 $[2M + Na]^+$. HRMS (IC, isobutane) calcd for $C_{17}H_{26}NO_4S$ $[M + H]^+$ 340.1582, obsd 340.1553.

2-[*N*-Fluorenylmethoxycarbonyl]amino 2-isopropylthio acetic acid, Fmoc-Gly(S-*i*Pr)-OH (1E) was synthesized as described.[22] Anal. Calcd for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.77. Found: C, 64.52; H, 5.75; N, 3.99.

2-[*N*-Fluorenylmethoxycarbonyl]amino 2-isopropylthio acetic acid benzyl ester, Fmoc-Gly(S-*i*Pr)-OBn (1F) was synthesized in 70% yield using the same protocol as for **1B**. Mp 102 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 1.32 (d, J = 6.7 Hz, 3H), 1.36 (d, J = 6.7 Hz, 3H), 3.21 (hept, J = 6.7 Hz, 1H), 4.24 (t, J = 7.0 Hz, 1H), 4.46 (d, J = 7.0 Hz, 1H), 5.22 (d, J = 12.2 Hz, 1H), 5.29 (d, J = 12.2 Hz, 1H), 5.50 (d, J = 9.2 Hz, 1H), 5.87 (d, J = 9.2 Hz, 1H), 7.32 (t, J = 7.3 Hz, 2H), 7.39 (bs, 5H), 7.43 (t, J = 7.4 Hz, 2H), 7.61 (d, J = 7.3 Hz, 2H), 7.78 (d, J = 7.4 Hz, 2H).^{13}C NMR (62.5 MHz, $CDCl_3$): δ 23.20, 23.81, 36.04, 46.94, 55.37, 67.19, 67.60, 76.50, 77.00, 77.53, 119.90, 124.92, 126.97, 127.64, 128.11, 128.42, 134.82, 141.17, 143.45, 143.58, 154.71,

169.10. HRMS (ESI) calcd for $C_{27}H_{27}NO_4SNa$ $[M + Na]^+$ 484.1558, obsd 484.1566.

General Protocol for Synthesis of A3G, 4. To a cooled solution (0 °C) of **1** (1 mmol) in dry THF (15 mL) under argon was rapidly added NBS (90 mgs, 0.51 mmol). After 30 min at 0 °C, **3** (1 mmol except for **b**, **e**, **f** where 2 mmol were used) was added, and the solution was stirred for 12 h. The resulting yellow oil was purified on silica gel (from heptane/EtOAc, 1/1 to heptane/EtOAc/AcOH, 1/1/0.05 or with CH_2Cl_2/EtOAc, 8/2 in the case of **b**, **e**, **f**, **m**) to afford **4** (Table 1). Spectral data are given in Supporting Information.

2-Acetamido 2-Acetoxy Acetic Acid Benzyl Ester Ac-Gly-(OAc)-OBn (5). Benzyl glyoxylate (100 mL in 50% MTBE, 0.45 mol), acetamide (13 g, 0.22 mol), and PTSA (1 g) were refluxed for 4 days in anhydrous THF (500 mL) in the presence of 3 Å molecular sieves. The solid residue from evaporation was triturated in Et_2O to give 14.2 g (0.064 mol, 29%) of *N*-acetyl α-hydroxy benzylglycinate, mp 107.5 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.97 (s, 3H), 5.26 (s, 2H), 5.64 (d, $J = 8.9$ Hz, 1H), 6.74 (d, $J = 8.9$ Hz, 1H), 7.48 (m, 5H), 8.96 (d, $J = 8.9$ Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6); 22.42, 65.98, 71.15, 127.82, 128.02, 128.17, 128.34, 135.73, 169.27, 169.76. MS (ESI): *m*/*z* 246.15 $[M + Na]^+$, 224.01 $[M + H]^+$.

This hydroxy derivative (10 g, 0.045 mol) in CH_2Cl_2 (180 mL) and pyridine (148 mL, 1.83 mol) was acetylated during 24 h with Ac_2O (224 mL, 2.37 mol). The crude residue was crystallized from a mixture of pentane/ether 90/10 to give 9 g (76%) of white solid, mp 142 °C. ^{1}H NMR (250 MHz, $CDCL_3$): δ 2.06 (s, 3H), 2.08 (s, 3H), 5.22 (s, 2H), 6.30 (d, $J = 9.1$ Hz, 1H), 6.9 (d, $J = 9.1$ Hz, 1H), 7.35 (m, 5H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.17, 59.75, 66.42, 127.66, 127.98, 128.32, 135.60, 145.59, 169.02, 169.57. MS (ESI): *m*/*z* 288.2 $[M + Na]^+$.

2-Acetamido 2-Anilino Acetic Acid Benzyl Ester Ac-Gly-(NH-Ph)-OBn (4Bm). Compound **5** (5 g, 18.86 mmol) in DMF (150 mL) containing aniline (1.93 g, 20.74 mmol) and TEA (5.32 mL, 73 mmol) was stirred for 16 h under argon. The solid resulting from evaporation was crystallized from EtOAc/pentane to afford 5.4 g (96%) of white powder, mp 145.5 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00 (s, 3H), 4.93 (d, $J = 7.2$ Hz, 1H), 5.32 (s, 2H), 6.02 (t, $J = 8.1$ Hz, 1H), 6.17 (d, $J = 8.1$ Hz, 1H), 6.69−7.33 (m, 5H), 7.42 (bs, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.50, 60.49, 68.25, 114.10, 119.62, 128.35, 128.72, 128.78, 129.60, 135.50, 144.1, 170.50. MS (ESI): *m*/*z* 321 $[M + Na]^+$, 337 $[M + K]^+$, 619.3 $[2M + Na]^+$. Calcd for $C_{17}H_{19}N_2O_3$ $[M + H]^+$ 299.1475, obsd 299.1461.

2-Acetamido 2-Anilino Acetic Acid Sodium Salt Ac-Gly-(NH-Ph)-ONa (4Am). Compound **4Bm** (1 g, 3.35 mmol) in dioxane (100 mL) was stirred with 0.5 N NaOH (6.6 mL, 3.3 mmol) for 16 h. The residue was dissolved in water (100 mL), and the aqueous phase was washed with EtOAc (2 × 20 mL). Evaporation of water afforded 0.55 g (2.64 mmol, 79%) of a white solid. ^{1}H NMR (200 MHz, D_2O): δ 1.92 (s, 3H), 5.43 (s,1H), 6.74−7.27 (m, 5H). ^{13}C NMR (50 MHz, pyridine-d_5): δ 22.08, 64.80, 113.04, 116.64, 128.4, 145.92, 173.76, 176.88. MS (ESI): *m*/*z* 209 $[M + H]^+$. HRMS (ESI) calcd for $C_{20}H_{22}N_4O_6Na$ $[2M - 2H + Na]^-$ 437.1437, obsd 437.1434.

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Supporting Information Available: Spectral data of all the new A3Gs **4Xx** synthesized according to the general protocol described above. This material is available free of charge via the Internet at http://pubs.acs.org.

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