Article

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Solution- and Solid-Phase Syntheses of Substituted Guanidinocarboxylic Acids

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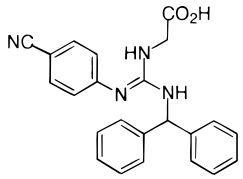
A library of guanidine-based compounds was produced to mimic the lead compound **1**, which is a substance known to have intensely sweet-taste characteristics. Libraries of guanidinocarboxylic acids were therefore prepared via two synthetic methods. The solid-phase method involving trapping of solution-phase carbodiimides by supported amines was used to produce *N*,*N*′-dialkyl derivatives (Scheme 1). The second solid-phase method, featuring supported carbodiimides and solution-phase amines (Scheme 2), was devised to prepare *N*,*N*′-disubstituted and *N*,*N*′,*N*′-trisubstituted guanidinocarboxylic acids. A small collection of guanadinoacetic acid dimers and trimers was also prepared, but this time via a solution-phase coupling of carbodiimides to a polyamine linker.

Introduction

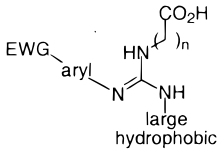
Applications of artificial sweeteners in society are widespread. The commonly used materials include aspartame (NutraSweet), sodium saccharin, acesulfame-K, and sucralose. However, there is still a need for an artificial sweetener that has the clean robust taste of sugar, remains stable in cooked foods, and has a long shelf life.[1]

Discovery of novel artificial sweeteners is challenging because the putative receptor(s) for sweet taste are unknown and have not been isolated by biochemical or cDNA cloning methods.[2−5] Typically, screening for sweetness is conducted by human-subject taste panels; hence, this is an inherently tedious and low-throughput process. However, monoclonal antibodies that "mimic" the sweet-taste receptor, in terms of compound immunoreactivity profiles, allow high-throughput fluorescence polarization assays to identify potentially sweet tasting compounds.[3] Fluorescence polarization is unique among methods used to analyze molecular binding because it gives a direct, nearly instantaneous measure of bound:free ligand ratios even in the presence of a free tracer. As a result, these assays can be performed with a single, premixed tracer-receptor reagent, eliminating the need for washing steps thereby making automation easier as well as reducing the total assay time.

The guanadinoacetic acid **1** is 300 000 times sweeter than 2% sucrose, as determined by human subject taste evaluations. It is a far more potent sweetener than aspartame, which is 180 times sweeter than 2% sucrose. Antibodies that are specific for compound **1** and that possess immunoreactivity profiles that are similar to the putative sweet-taste receptor are now available that facilitate screening of libraries via high-throughput fluorescence polarization techniques.[3,6,7] This paper concerns production of a small focused library to screen in that assay.



1 (NC-174)



A

Several solid-phase syntheses of guanidines have been reported, but most are not ideal for compound **1** analogues. For instance, many of the reported syntheses cannot readily be adapted to give one substituent on each guanidine-nitrogen.[4,5,8−10] Other methods do not have this limitation, but involve other restrictions. Those that feature additions of amines to carbodiimides (in solution or on a solid phase), for instance, tend to require the carbodiimide, and therefore the product guanidine, to be substituted with acyl or carbamoyl groups.[4,11,12] However, it was desirable to prepare analogues of **1** that do not have such N-substituents.

This paper describes new high-throughput syntheses of guanidines that do not have the limitations discussed above. The methods developed were used to prepare a focused library of guanidine derivatives similar to **1**, since structure−activity data from prior studies indicated that some functionalities of **1** were essential for sweet-taste characteristics.

Results and Discussion

Syntheses of Guanidinoacetic/propionic Acids via Reactions of Supported Amines with Carbodiimides in Solution. Scheme 1 outlines a synthesis of guanidines that involves preparations of carbodiimides in solution and then reactions of these with anchored amines. Most of this sequence is well-known solution-phase chemistry, but the particular protocol established here is extremely practical. Many isothiocyanates are commercially available, and others can be made easily by combination of amines with thiophosgene.[13] These isothiocyanates react readily with amines

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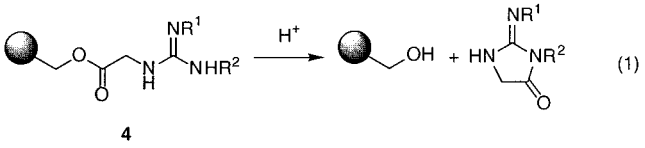
to give thioureas **2**. Isolation of the thioureas **2** tends to be trivial since most of these products are practically insoluble in ether and are easily purified by washing with that solvent. Conversion of thioureas to carbodiimides on treatment with Mukaiyama's reagent (2-chloro-1-methypyridinium iodide) is almost instantaneous at room temperature,[4,11] though brief sonication was desirable to accelerate solubilization of Mukiayama's reagent. The carbodiimides **3** are very nonpolar and are generally isolated by extraction into hexanes and filtration through a short silica plug using the same solvent. Reaction times for addition of the carbodiimides to Wang-supported glycine or β-alanine varied, but the transformation was conveniently monitored via the ninhydrin test.[14]

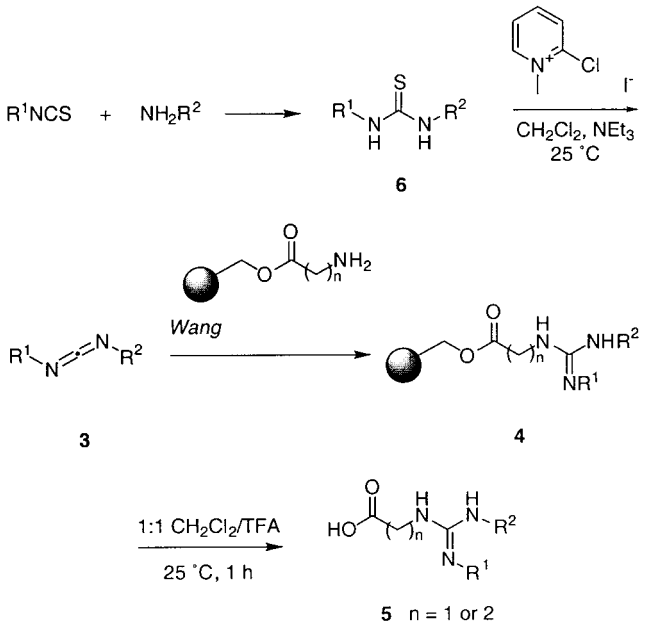
Table 1 shows data collected for specific compounds prepared via the sequence shown in Scheme 1. A limitation of this method was that the supported guanidines **4** tended to undergo an undesired intramolecular cyclization, as shown in reaction 1. We believe this occurs predominantly under acidic conditions during cleavage of the product from the resin;[15,16] it is only possible for primary amines. Some trends were evident with respect to this side reaction. First, it became more prevalent when the amine was relatively unhindered. Second, guanadinoacetic acid derivatives were more inclined to participate in this process than guanidinopropionic acids; in fact, cyclized byproducts were minimal in the latter case (compare Table 1, entries 2 vs 21 and 6 vs 24). Presumably, the undesirable ring formation is faster for five-membered than for six-membered rings. Third, the cyclization was suppressed when the substituents contained strongly electron-withdrawing groups. The cyclization (1) appears to occur both on the solid phase and in solution; for example, when the purified compounds were allowed to stand in solution this reaction proceeded. Indeed, cyclic impurities form when the guanidines **5** are allowed to stand for extended periods at room temperature.



4

Syntheses of Guanidinoacetic Acids via Resin-Bound Carbodiimide Intermediates. The method described above is appropriate for synthesis of variously substituted guanidinoacetic/propionic acids. However, there are two limitations associated with it. First, the method requires preparation of individual carbodiimides in solution, and second, guanidinoacetic acids with two substituents on one nitrogen atom are not available because the carbodiimide can only be formed from primary amines. Thus an alternative method was developed to expand the scope of our study. Scheme 2 shows how guanidines **9** were prepared from glycine on Wang resin through a resin-bound carbodiimide intermediate. 4-Cyanophenyl-, 4-nitrophenyl-, and 4-chlorophenyl-isothiocyanate were reacted with this resin to give three supported thioureas **6**. Various methods were investigated to affect conversion of these thioureas to anchored carbodiimides, and Mukaiyama's reagent gave especially good results. In the case of the 4-chlorophenyl derivative, production of the

Scheme 1



supported carbodiimide intermediate **7** (Y = Cl) was confirmed by on-resin IR (2133 cm^{-1}).[17] The putative resin-bound carbodiimide intermediates were reacted with a series of primary and secondary amines to give the products. Table 2 is a collection of data regarding the specific compounds made by this method.

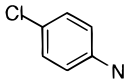
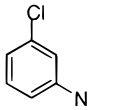
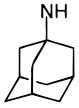
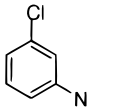
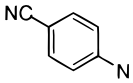
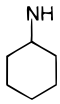
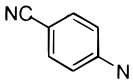
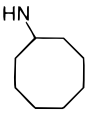
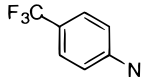
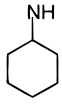
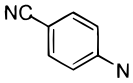
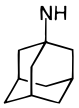
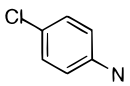
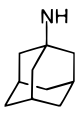
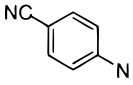
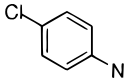
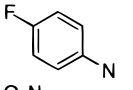
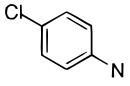
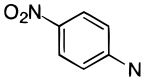
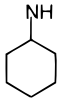
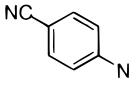
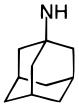
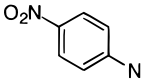
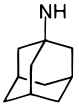
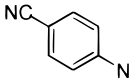
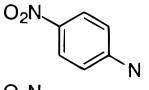
Review of Table 2 reveals that the products were generally formed in high purities, when alkylamines were used. This method was a practical and effective approach to the compounds shown and was highly satisfactory for the current work. However, an aromatic amine gave an inferior result (entry 18), hence more reactions with this type of amine were not attempted.

Two limitations of the method became evident. These did not restrict the current study, but we mention them here in case others should wish to expand and modify this methodology. First, when aryl isothiocyanates without at least one electron-withdrawing group on the aromatic ring were used, the corresponding carbodiimide was less electron-deficient, and addition of amines to it were less facile. Indeed, it may be necessary to heat the reaction to get the addition to proceed. Second, when primary amines were added to the supported carbodiimides, the side reaction 1 (vide supra) occurred, giving molecular ion MS peaks at 18 Da less than the expected values, and tended to be the most significant factor leading to diminished purities.

Parallel Solution-Phase Syntheses of Guanidinoacetic Acids Dimers. A set of six dimeric and two trimeric guanidonacetic acid derivatives based on structure A was also prepared. The motivation behind this part of the study was as follows. Since the structure of the sweet-taste receptor is unknown, it is possible that oligomeric structures may bind two or more "hot-spots" on the receptor surface simultaneously. This might in turn lead to stronger binding and higher bioactivities.

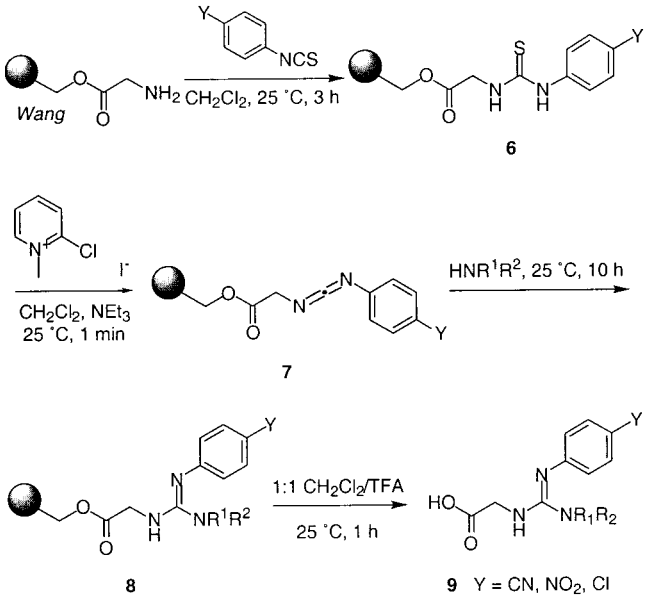
Scheme 3 shows the solution-phase approach adopted for the preparation of this library. Throughout, a tertiary butyl group was used to mask the carboxylic acid. Thus, thioureas

Table 1. Guanidinoacetic/propionic Acids **5** Prepared from Carbodiimides in Solution

entry	n	NR^1	NHR^2	HPLC purity[a] (%)	crude yield (%)	entry	n	NR^1	NHR^2	HPLC purity[a] (%)	crude yield (%)
1	1			87	53	17	1			70	77
2	1			80	85						
3	1			64	85	18	1			78	91
4	1			65	78	19	1			96	66
5	1			71	75	20	1			90	77
6	1			94	90	21	2			96	93
7	1			60	69	22	2			61	71
8	1			65	82	23	2			58	78
9	1			74	80	24	2			98	96
10	1			92	93	25	2			76	85
11	1			80	86	26	2			55	63
12	1			75	85	27	2			95	92
13	1			85	91	28	2			99	76
14	1			98	84	29	2			72	80
15	1			97	83	30	2			92	89
16	1			53	74	31	2			88	94

[a] Monitored by UV at 215 nm; molecular ions were detected for all compounds via MALDI-MS.

Scheme 2



10 and carbodiimides **11** were obtained by methods analogous to those described above (Scheme 2). Compounds **11** were purified by filtration through silica and were obtained in satisfactory yields. The reaction of diamines and triamines with these carbodiimides in dichloromethane was smooth, but the products **12** had to be purified via flash chromatography. After the purification, the dimers (trimers) **13** were obtained by acidic hydrolysis. Unfortunately, further purification of these materials was impractical due to their polarity; however, their purities after the acidic deprotection step were satisfactory for preliminary screens (Table 3). Once again, the unwanted cyclization reaction 1 was observed when a primary diamine was used.

Conclusions

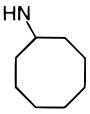
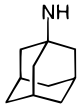
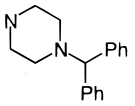
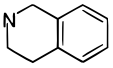
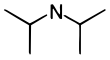
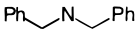
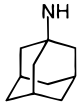
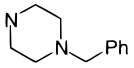
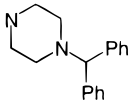
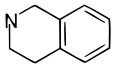
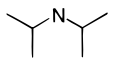
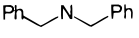
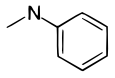
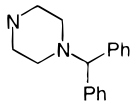
The methods outlined here for preparations of guanidinocarboxylic acids facilitate screening for analogues of the superpotent sweetener compound **1** via fluorescence polarization immunoassays, as an initial screening procedure before evaluation by a human-panel taste threshold test. The methods shown in Schemes 1 and 2 feature supported reagents for ease of purification and highly efficient solution-phase steps wherein the products can be isolated by precipitation. The route developed in Scheme 3 is exclusively solution-phase reactions, but no difficult purification is required. All these syntheses could be automated to enable larger libraries to be produced, though some manually executed solution-phase reactions might be necessary to prepare key reagents. Fluorescence polarization assays and human taste panel tests on these libraries are now in progress.

Experimental Section

General Information. Fmoc deprotection was performed by treating the resin with 20% piperidine in DMF twice for 5 and 10 min each. The washing and drying protocol was as follows: DMF, methanol, DMF, methanol, dichloromethane, methanol, dichloromethane, and vacuum-drying overnight.

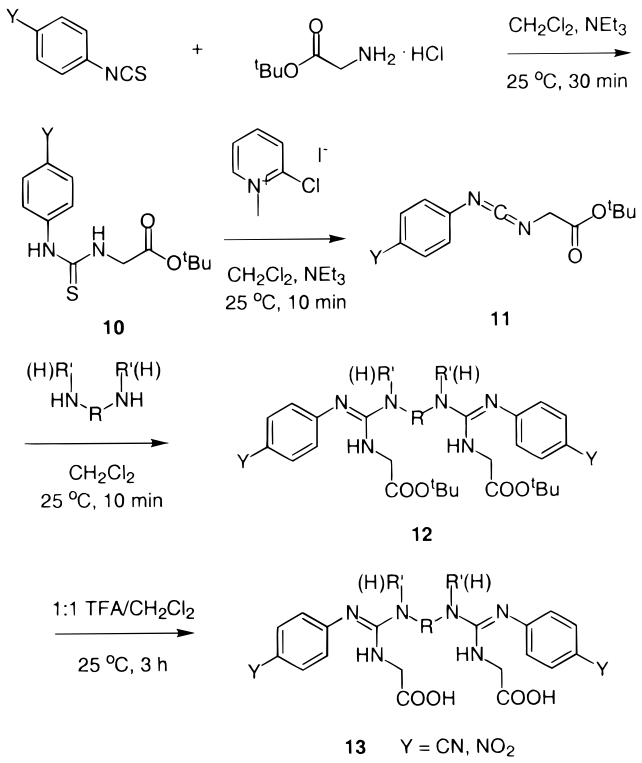
General Procedure for Syntheses of Guanidinoacetic/propionic Acids via Reactions of Supported Amines with

Table 2. Preparation of Guanidinoacetic Acids **9** via Supported Carbodiimides

entry	Y	NR^1R^2	HPLC purity[a] (%)	crude yield (%)
1	CN		87	68
2	CN		63	78
3	CN		93	73
4	CN		95	56
5	CN		80	87
6	CN		99	76
7	CN		94	85
8	CN		80	91
9	CN		99	82
10	NO_2		86	80
11	NO_2		96	87
12	NO_2		90	94
13	NO_2		95	86
14	NO_2		96	94
15	NO_2		97	84
16	NO_2		86	83
17	NO_2		91	71
18	NO_2		<50	-
19	Cl		94	84

[a] Monitored by UV at 215 nm; molecular ions were detected for all compounds via MALDI-MS.

Scheme 3

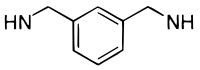
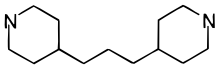
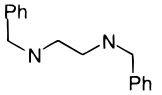
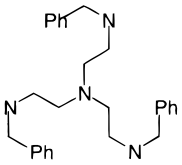
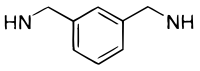
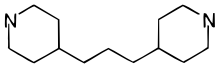
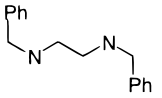
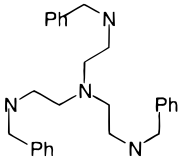


Carbodiimides in Solution. The requisite carbodiimides were prepared by the following general protocol. Equal amounts of a primary amine and an isothiocyanate (usually 0.5 mmol) were mixed in 10 mL of dichloromethane. The formation of the thiourea was generally rapid (TLC), except for aromatic amines, in which case the reactions proceeded at a more convenient rate at 40 °C. After complete formation of the thiourea (TLC), the solvent was removed and the resulting solid was washed several times with 1:1 ether/petroleum ether and then dried in vacuo. The thiourea thus obtained is typically obtained in a high state of purity and is used *as is* in the next synthetic step.

Conversion of the thioureas to the carbodiimides was via the following procedure. The thioureas prepared as above were dissolved in 10 mL of dichloromethane. Five equivalents of triethylamine, then 1 equiv of the Mukaiyama's reagent were added, and the reaction mixture was briefly sonicated to obtain a homogeneous solution. The formation of the carbodiimide was fast, usually within 1 min (by TLC). The solvent was then removed, and small amount of hexanes (or petroleum ether) was added. The carbodiimide, but not the byproducts, was generally soluble in this solvent. The hexanes solution was then passed through a short pad of silica gel packed in a pipet. This effectively removed impurities and give practically pure carbodiimide as a viscous liquid or a low melting point solid. For the 4-nitrophenyl derivatives, the carbodiimides were not soluble in petroleum ether or hexanes; in those situations 25% diethyl ether/hexanes was used in place of pure hexanes.

Some proton NMR data of illustrative examples are as follows. *N*-4-Chlorophenyl-*N*′-1-adamantal carbodiimide: ^{1}H NMR ($CDCl_3$) δ 7.23 (d, $J = 9.0$ Hz, 2H), 7.00 (d, $J = 9.0$ Hz, 2H), 2.12 (bs, 3H), 1.92 (bs, 6H), 1.67 (bs, 6H). *N*-4-Chlorophenyl-*N*′-2,2-diphenylethyl carbodiimide: ^{1}H NMR ($CDCl_3$) δ 7.40−7.20 (m, 10H), 7.10 (d, $J = 8.9$ Hz, 2H), 6.50 (d, $J = 8.9$ Hz, 2H), 4.37 (t, $J = 7$ Hz, 1H), 4.03 (d, $J = 7$ Hz, 2H). *N*-Pentafluorophenyl-*N*′-diphenylmethyl carbodiimide: ^{1}H NMR ($CDCl_3$) δ 7.46−7.30 (m, 10H), 6.07 (s, 1H).

Table 3. Guanidinoacetic Acids Dimers

entry	Y	(H)R'NRNR'(H)	HPLC purity[a] (%)	Crude yield (%)
1	CN		60	74
2	CN		73	67
3	CN		80	67
4	CN		74	26
5	NO_2		72	77
6	NO_2		95	92
7	NO_2		87	18
8	NO_2		80	16

[a] Monitored by UV at 215 nm; molecular ions were detected for all compounds via MALDI-MS.

The following protocol was used for reaction of the resin-bound amines with the carbodiimides in solution. Fmoc-Gly-Wang resin (ChemImpex) or Fmoc-β-Ala-Wang resin (homemade) was deprotected by 20% piperidine in DMF. After washing and drying, the resin was suspended in DMF and the carbodiimide (3−4 equiv) dissolved in DMF was added. The whole was agitated for a certain period of time depending on the reactivity of the carbodiimide. In most cases the reaction was completed in 1 h, as checked by the ninhydrin test. Compounds having the 1-adamantyl substituent and no strong electron-withdrawing group on the carbodiimide had to be heated to 50 °C for longer reaction times. After the reaction was completed, the resin was washed and dried. The cleavage was accomplished by treating the resin with 1:1 TFA/dichloromethane at room temperature for 1 h. The product was obtained by evaporation of solvents.

General Procedure for Syntheses of Guanidinoacetic Acids via Resin-Bound Carbodiimide Intermediates. The following procedure was used to synthesize the guanidinoacetic acids. Fmoc-Gly-Wang resin (ChemImpex) was

deprotected with 20% piperidine in DMF. After washing and drying, the resin was suspended in dry dichloromethane and treated with 2−3 equiv of the corresponding isothiocyanate (Y = CN, NO_2, Cl). After 3 h of agitation at room temperature, the resin was washed and dried. It was then suspended in 1:1 DMF and dichloromethane, and 5 equiv of triethylamine was added. Two equivalents of Mukaiyama's reagent was then added, and the resin was briefly agitated (about 1 min.). An amine (primary or secondary, 5 equiv) was then added, and the resin was agitated for 10 h at room temperature (in case of Y = Cl, the reaction was carried out at 50 °C). This was then washed and dried. The cleavage was accomplished by treating the resin with 1:1 TFA/dichloromethane at room temperature for 1 h, and the product was collected by evaporation of the solvents.

General Procedure for Parallel Solution-Phase Syntheses of Guanidinoacetic Acid Dimers. The synthesis of *N*-aryl-*N*′-*tert*-butoxycarbonylmethyl carbodiimide intermediate is as follows. Equimolar amounts (5 mmol) of glycine *tert*-butyl ester hydrochloride and the appropriate aryl isothiocyanate were mixed in 10 mL of dichloromethane with 5 equiv of triethylamine. The formation of thiourea in this reaction was monitored by TLC. After completion (usually around 30 min), the solvent was removed and the residue was dissolved in ethyl acetate and washed with water. Drying and evaporation gave the thiourea as a white (Y = CN) or yellow (Y = NO_2) solid. The thiourea was then dissolved in dichloromethane, and 3 equiv of triethylamine were added. This was followed by addition of Mukaiyama's reagent (1.2 equiv). The mixture was sonicated briefly and stirred at room temperature for 10 min. TLC showed the reaction was generally complete in less than 10 min. The solvent was removed, and the residue was passed through a short column of silica gel, eluting with 1:1 petroleum ether and dichloromethane. This gave the carbodiimide as a viscous liquid; this sometimes solidified on standing at room temperature for extended periods. Yield: 65% (two steps, Y = CN, white solid); 83% (two steps, Y = NO_2, yellow solid). *N*-4-Cyanophenyl-*N*′-*tert*-butoxycarbonylmethyl carbodiimide: ^{1}H NMR ($CDCl_3$) δ 7.54 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 3.98 (s, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 167.8, 145.3, 135.9, 133.3, 124.8, 118.9, 107.8, 83.3, 47.9, 28.0. *N*-4-Nitrophenyl-*N*′-*tert*-butoxycarbonylmethyl carbodiimide: ^{1}H NMR ($CDCl_3$) δ 8.11 (d, J = 8.9 Hz, 2H), 7.25 (d, J = 8.9 Hz, 2H), 4.00 (s, 1H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 167.7, 147.5, 144.4, 135.5, 124.9, 124.4, 83.3, 47.9, 27.9.

The following protocol was used to prepare guanidinoacetic acid dimers and trimers. A dichloromethane solution (about 0.05 M) of the carbodiimide (2.2 equiv, 3.3 equiv in case of trimers) and 1.0 equiv of the diamine (or triamine) was stirred at room temperature for 5 h, or until completion of the reaction (TLC). The solvent was removed, and the residue was passed through a silica gel column first, eluting with 1:1 ether/dichloromethane to remove apolar impurities, and then the product **12** was obtained as viscous oil by eluting with 10% methanol in dichloromethane. This oil was then treated with 1:1 TFA/dichloromethane for 3 h at room temperature to hydrolyze the *tert*-butyl ester. Removal of the solvents gave the product diacids or triacids **13**, as viscous syrupy materials.

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Supporting Information Available. NMR spectra of selected compounds from Tables 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Ager, D. J.; Pantaleone, D. P.; Henderson, S. A.; Katritzky, A. R.; Prakash, I.; Walters, D. E. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1802−1817.
(2) DuBois, G. E.; Walters, D. E.; Kellogg, M. S. In *Flavor Measurement*; Ho, C.-T., Manley, C. H., Eds.; M. Dekker: New York, 1993; pp 239−266.
(3) Carpenter, R.; Anchin, J. M.; Linthicum, D. S. *Hybridoma* **1996**, *15*, 17−21.
(4) Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *J. Org. Chem.* **1997**, *62*, 1540−1542.
(5) Wang, F.; Hauske, J. R. *Tetrahedron Lett.* **1997**, *38*, 8651−8654.
(6) Anchin, J. M.; Droupadi, P. R.; DuBois, G. E.; Kellogg, M. S.; Nagarajan, S.; Carter, J. S.; Linthicum, D. S. *J. Immunol.* **1994**, *153*, 3059−3069.
(7) Sulikowski, M.; Kim, K.; Sulikowski, G. A.; Nagarjan, S.; Linthicum, D. S. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2875−2878.
(8) Dodd, D. S.; Wallace, O. B. *Tetrahedron Lett.* **1998**, *39*, 5701−5704.
(9) Robinson, S.; Roskamp, E. J. *Tetrahedron* **1997**, *53*, 6697−6705.
(10) Ostresh, J. M.; Schoner, C. C.; Hamashin, V. T.; Nefzi, A.; Meyer, J.-P.; Houghten, R. A. *J. Org. Chem.* **1998**, *63*, 8622−8623.
(11) Josey, J. A.; Tarlton, C. A.; Payne, C. E. *Tetrahedron Lett.* **1998**, *39*, 5899−5902.
(12) Lin, P.; Ganesan, A. *Tetrahedron Lett.* **1998**, *39*, 9789−9792.
(13) Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron* **1981**, *37*, 233−284.
(14) Sarin, V. K.; Kent, S. B. H.; Tam, J. P.; Merrifield, R. B. *Anal. Biochem.* **1981**, *117*, 147−157.
(15) Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933−5936.
(16) Schneider, S. E.; Bishop, P. A.; Salazar, M. A.; Bishop, O. A.; Anslyn, E. V. *Tetrahedron* **1998**, *54*, 15063−.
(17) Nelson, J. C.; Young, J. K.; Moore, J. S. *J. Org. Chem.* **1996**, *61*, 8160−8168.

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