ChemPubSoc Europe

DOI: 10.1002/ejoc.201600137

EurJOC European Journal of Organic Chemistry

Communication

Deltic Compounds

Macrosteres: The Deltic Guanidinium Ion

Kenji Mishiro,[a] Fanghao Hu,[a] Daniel W. Paley,[a] Wei Min,[a] and Tristan H. Lambert*[a]

Abstract: The "deltic guanidinium" ion is described here as a "macrostere" of the guanidinium ion. The use of the 2,4-dimethoxybenzyl protecting group allows for the synthesis of the fully unsubstituted parent compound and a variety of derivatives bearing multiple N–H functions for the first time. Deltic urea, deltic thiourea, and deltic benzamidine are also synthesized. A comparison of the physical properties of guanidinium and deltic guanidinium ions is provided. The use of a deltic guanidinium dendrimer for cell transport is demonstrated.

Introduction

An isostere is a functional group that mimics certain characteristics of another functional group, such as the number of valence electrons, steric size, or biological effect.[1] In the realm of medicinal drug discovery, the use of "bioisosteres" to retain the desired biological activity of a drug candidate while optimizing its overall pharmacological profile is a widely employed strategy.[2,3] However, isosteric replacement can be challenging for certain functional groups in which modification tends to result in major phenomenological changes. A key example in this regard is the guanidinium ion,[4] where the low acidity, high hydrogen-bond donating capacity, and stable cationic nature make it difficult to replicate (Figure 1a).[5] Nevertheless, because guanidinium ions occur widely in a variety of important settings, including biomolecules,[6] complex secondary metabolites,[7] pharmaceutical drugs,[8] sweeteners,[9] and many other useful chemicals,[10] the identification of new isosteres of this important functional group has wide-ranging implications. Herein, we describe the first guanidinium ion "macrostere", which retains all of the essential features of the guanidinium ion but is simply expanded in size. In this macrostere, the central carbon atom of the guanidinium ion is replaced with a cyclopropenium ion, and is thus termed the "deltic guanidinium ion".[11]

The deltic guanidinium ion is in essence a triaminocyclopropenium (TAC) ion. Although highly substituted TACs are known,[12,13] derivatives possessing more than a single N–H moiety are not available by established methods, because primary amines or ammonia induce ring-opening of the strained cyclopropenium ring (Figure 1b).[14] Fully substituted deltic guanidinium ions, however, can be easily prepared by the addition of amines to tetrachlorocyclopropene or pentachlorocyclopropane.[15] Thus, in order to develop a viable approach to less-

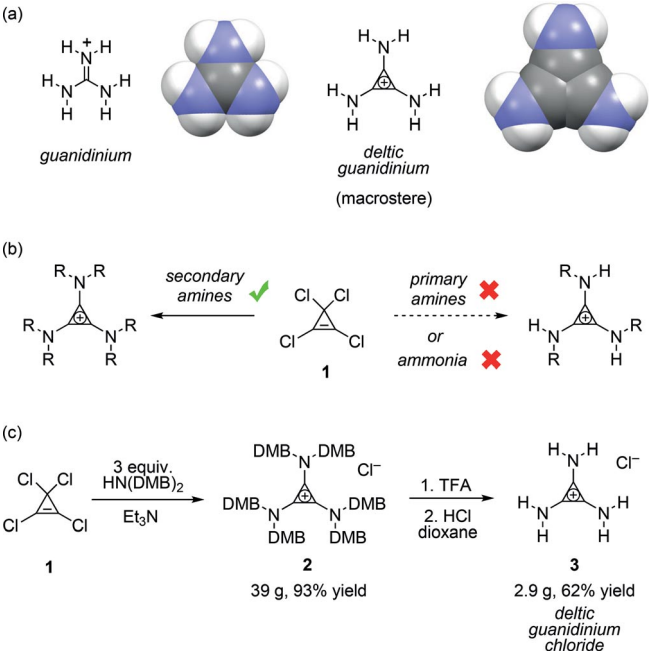


Figure 1. (a) Guanidinium and the deltic guanidinium macrostere. (b) Synthesis of triaminocyclopropenium (detlic guanidinium) ions. (c) Synthesis of deltic guanidinium chloride. DMB = 2,4-dimethoxybenzyl.

substituted deltic guanidinium ions, we needed to identify a suitable nitrogen protecting group that would allow a primary amine or ammonia derivative to be installed and deprotected without destroying the cyclopropenium ring. After some experimentation, we found that the acid-labile 2,4-dimethoxybenzyl (DMB) group offered ready access to the desired compounds, typically without the need for column chromatography.[16] For example, addition of 3 equiv. of $HN(DMB)_2$ to tetrachlorocyclopropene (**1**) in the presence of triethylamine resulted in the formation of compound **2** in 93 % yield on a preparative scale (Figure 1c). Acidic deprotection of **2** with TFA followed by ion exchange with HCl in dioxane then furnished deltic guanidinium chloride (**3**) in 62 % yield. This result represents the first reported synthesis of this macrostere of the guanidinium ion

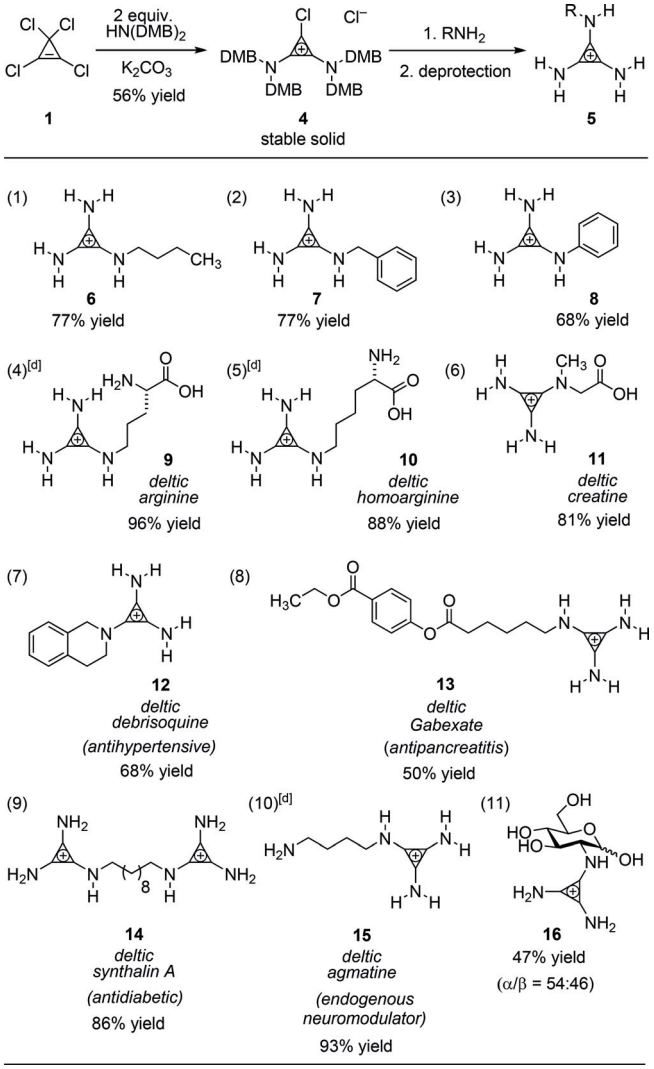
[a] *Department of Chemistry, Columbia University*
3000 Broadway, New York, NY 10027, USA
E-mail: tl2240@columbia.edu
http://www.columbia.edu/cu/chemistry/groups/lambert/
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/ejoc.201600137.

and sets the stage for a detailed comparison of the two (vide infra).

Results and Discussion

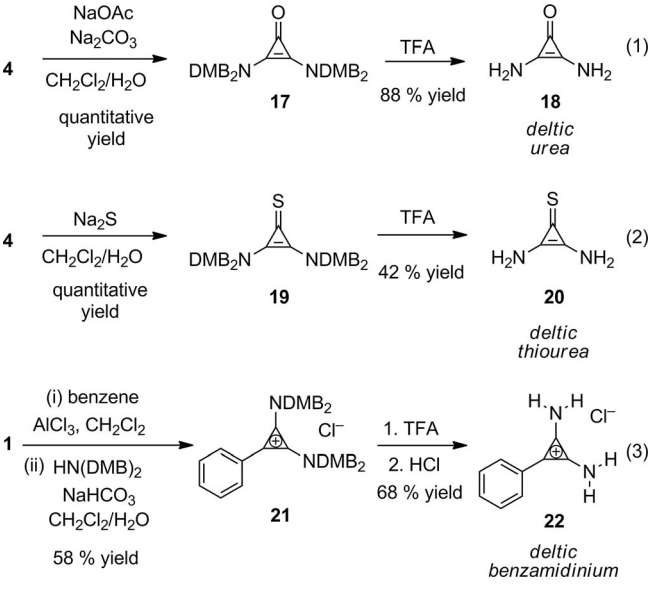
We also found that derivatives of the deltic guanidinium ion could be prepared in a straightforward fashion (Table 1). For example, treatment of **1** with 2 equiv. of $HN(DMB)_2$ in the presence of K_2CO_3 resulted in the production of the stable 1-chloro-2,3-bis(dialkylamino)cyclopropenium salt **4** in 56 % yield. This salt reacted efficiently with amines to produce, following deprotection and anion exchange, the corresponding deltic guanidinium derivatives **5**. Using this approach, deltic guanidiniums bearing alkyl (**6**), benzyl (**7**), or aryl (**8**) substituents (Entries 1–3) were prepared in high yield. Amino acid analogues of arginine (**9**; Entry 4), homoarginine (**10**; Entry 5), and creatine (**11**; Entry 6) were also prepared by these means. We have also prepared macrosteric analogues of the antihypertensive agent debrisoquine[17] (**12**; Entry 7), gabexate (**13**; Entry 8), which is used in antipancreatitis treatment,[18] synthalin A (**14**; Entry 9), a bis(guanidinium) compound that has antidiabetic activity,[19] and agmatine, an endogenous neurotransmitter,[20] (**15**; Entry 10). Finally, this synthetic strategy was mild enough to allow for the preparation of the deltic guanidinium derivative **16** of glucosamine (Entry 11).[21]

Table 1. Synthesis of deltic guanidinium derivatives.[a,b]



[a] See the Supporting Information for synthetic details. [b] Counterions are chloride, except for Entries 7 and 11, which are trifluoroacetate. [c] The activities indicated in parentheses are for the corresponding guanidinium derivatives. [d] Isolated as the protonated ammonium salts.

We found that this strategy could also be adopted to access other deltic macrosteres as well. For example, hydrolysis of **4** under basic conditions followed by deprotection furnished deltic urea **18** in 88 % yield [Equation (1)]. Alternatively, treatment of **4** with Na_2S followed by deprotection yielded deltic thiourea **20** [Equation (2)]. Friedel–Crafts alkylation of benzene with tetrachlorocyclopropene followed by addition of $HN(DMB)_2$ produced cyclopropenium compound **21**, and thus allowed access to deltic benzamidinium derivative **22** [Equation (3)]. We expect that these procedures should be adaptable to access substituted derivatives of this deltic functionality as well.



To evaluate their isosteric similarity, we compared several of the physical properties of the guanidinium and deltic guanidinium ions (Table 2). In terms of acidity, the high pK_a (H_2O) value of 13.5 is a widely recognized key aspect of the guanidinium ion's behavior, particularly in a biochemical context. We determined the aqueous pK_a value of the deltic guanidinium ion to be notably higher at 15.5 (Entry 2). Of course, practically speaking, these low acidities mean that both guanidinium and deltic guanidinium ions will tend to remain fully protonated under physiological conditions. Notably, all of the deltic analogues were found to be stable in water, and should thus be useful for biological studies.

As a cation with six hydrogen-bonding sites, guanidinium chloride is also extremely water-soluble, at approximately 230 g/100 mL (Entry 3). We found that deltic guanidinium chloride is less than one-third as soluble in water at 90 g/100 mL, which is nevertheless also very high. Interestingly, we found that, while guanidinium chloride is also quite soluble in ethanol

Table 2. Comparison of physical properties of guanidinium and deltic guanidinium ions.

Entry	Property			R
1	mol. weight (g/mol)	95.53	119.55	H
2	pK_a (H_2O)[a]	13.5	15.5	
3	H_2O solubility (g/100 mL)[b]	230	90	
4	EtOH solubility (g/100 mL)[b]	22	1.3	
5	log *D* (pH = 7.4)[b,c]	0.39	0.56	

[a] 27 °C. [b] 23 °C. [c] *n*-octanol/PBS buffer.

(22 g/100 mL), the deltic analogue was significantly less so at only 1.3 g/100 mL (Entry 4). To compare the relative lipophilicities of the two cations, we measured the distribution coefficient log *D* (*n*-octanol/PBS buffer, pH = 7.4) of [(1-naphthyl)methyl]guanidinium and deltic guanidinium ions, and found their values to be very similar, with the deltic isostere being slightly more lipophilic (Entry 5).

As a further characterization of deltic guanidinium chloride, we also obtained its solid-state Raman spectrum.[22] An overlay of this spectrum (red) and that of guanidinium chloride (blue) is shown in Figure 2. The most notable difference between the two is the deltic guanidinium peak at 1998 cm^{-1}, which corresponds to the symmetric ring stretching vibration of the cyclopropenium ring (inset box).[23] Because this peak occurs in the biologically silent region of the Raman spectrum, we speculate that deltic guanidinium derivatives may be useful for Raman-based biological imaging applications.[24]

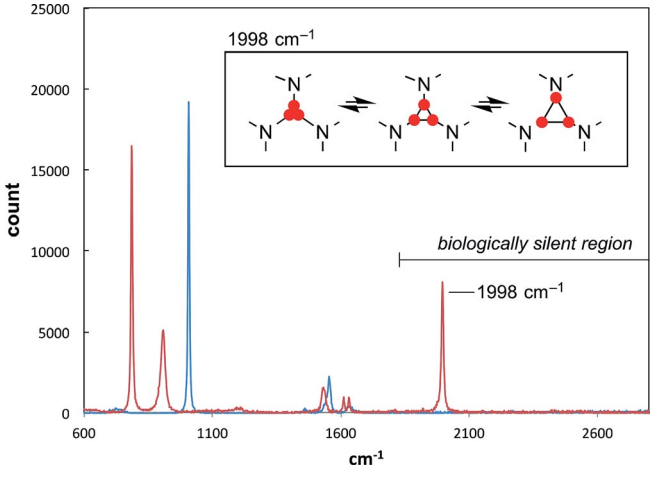


Figure 2. Raman scattering spectrum of guanidinium chloride (blue trace) and deltic guanidinium chloride (red trace).

To further the functional comparison of the guanidinium and deltic guanidinium ions, we determined single-crystal X-ray structures for several salts of the latter (Figure 3). Deltic guanidinium choride crystallizes in a rhombohedral structure ($R\bar{3}c$), forming six equivalent hydrogen bonds to chloride ions (Figure 3a), and with each chloride ion in turn hydrogen-bonding to six $C_3N_3H_6$ cations (not shown). This highly symmetric structure differs from the lower-symmetry, orthorhombic (*Pbca*) structure of guanidinium chloride, in which each cation associates with three anions through two-point hydrogen-bonding interactions (Figure 3b). On the other hand, deltic guanidinium iodide has a cubic structure ($Pa\bar{3}$), with the coordination of three iodide ions by cooperative pairs of hydrogen bonds strongly resembling the structure of guanidinium chloride (Figure 3c). Clearly, the deltic guanidinium ion offers an expanded hydrogen-bonding pocket that can accommodate a larger anion such as iodide.

Guanidinium-rich molecules such as polyarginine peptides are known to promote cell-membrane transportation,[25] and the application of this phenomenon to drug delivery and transfection has been actively researched.[26] Thus, we were interested to see whether polydeltic guanidinium ion containing molecules would also operate as membrane transportation agents. To do so, fluorescein-coupled dendrimers having 3, 6, or 9 deltic guanidinium units (**ΔG3**, **ΔG6**, **ΔG9**) were synthesized in direct analogy to the known[27] guanidininium-rich dendrimers (**G3**, **G6**, **G9**) (Figure 4a),[7] and an imaging experiment of their intracellular translocation was conducted (Figure 4b). The membrane transportation activity of both the deltic guanidinium and guanidinium dendrimers was evaluated in live HeLa cells. Neither the tricationic (**G3** and **ΔG3**) nor the hexacationic (**G6** and **ΔG6**) dendrimers resulted in observable membrane transportation. However, a further increase to the nonacationic dendrimers (**G9** and **ΔG9**) promoted entry into the cells, with strong intracellular fluorescence observed in both

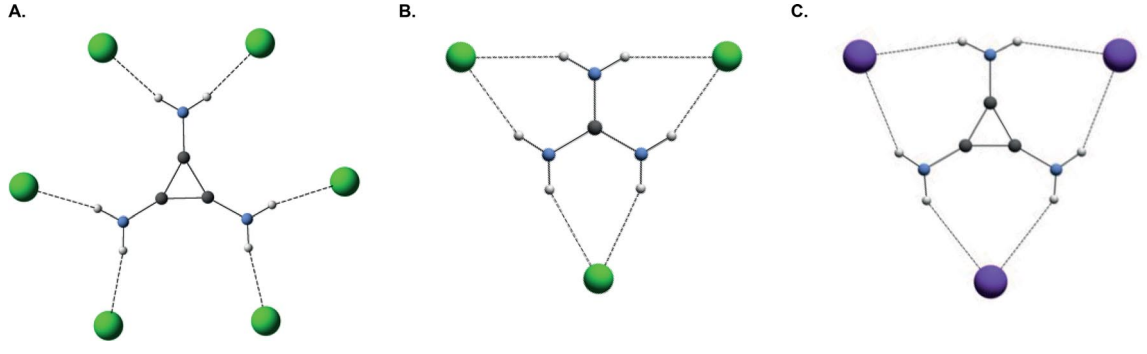


Figure 3. Molecular structures of (a) deltic guanidinium chloride, (b) guanidinium chloride, and (c) deltic guanidinium iodide.

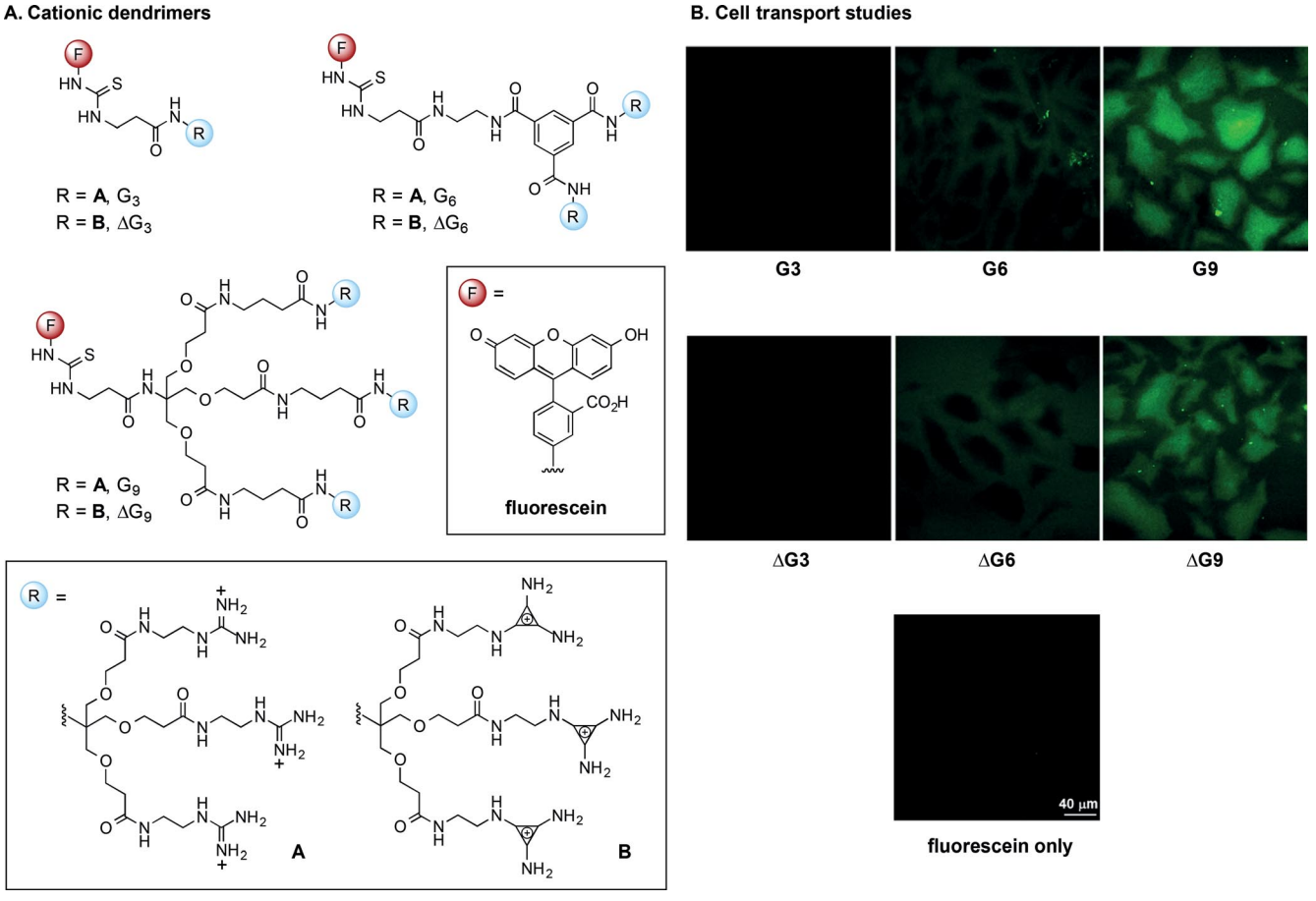


Figure 4. (a) Fluorescein-coupled dendrimers incorporating guanidinium or deltic guanidinium ions. (b) Cell-transport studies with cationic dendrimers.

cases. We thus conclude that deltic guanidinium ions possess membrane transportation ability qualitatively similar to the guanidinium group, despite their differences in hydrogen-bond organization.

Conclusions

The guanidinium ion is a crucial ingredient in the chemistry of life and in numerous valuable chemicals. As a "macrostere" of this important functional group, the deltic guanidinium represents a unique guanidinium analogue, which mimics certain properties of this functionality in ways other isosteres cannot. Undoubtedly, the increased size of the deltic guanidinium ion will make it a poor replacement in compounds where binding of the guanidinium ion is a key aspect of the desired bioactivity. On the other hand, this expanded analogue could be useful in circumstances in which the molecular properties engendered by the guanidinium ion are desired, but off-target interactions (e.g. with arginine-binding enzymes) must be eliminated. More broadly, the concept of the macrostere offers a unique strategy for creating "deltic" analogues of any functional group that possesses a central sp^2-hybridized carbon atom. A broad investigation of these deltic functional groups can now be undertaken, and such studies are underway in our laboratory.

Acknowledgments

Financial support for this work was provided by the National Institute of General Medical Sciences (NIGMS) (R01 GM102611). W. M. is grateful for support from the National Institutes of Health (NIH) (R01 EB020892). K. M. is grateful for support from the Japan Society for the Promotion of Science (JSPS) Postdoctoral Fellowship for Research Abroad, the Uehara Memorial Foundation Research Fellowship, and the Kyoto University Foundation Fellowship for Research Abroad. Single-crystal X-ray diffraction was performed at the Shared Materials Characterization Laboratory (SMCL) at Columbia University. Use of the SMCL was made possible by funding from Columbia University. T. H. L. thanks Prof. Paul Wender (Stanford University) and Prof. Viresh Rawal (University of Chicago) for helpful discussions.

Keywords: Isosteres · Guanidinium · Cyclopropenium · Aromaticity · Medicinal chemistry

[1] a) I. Langmuir, *J. Am. Chem. Soc.* **1919**, *41*, 1543; b) H. Erlenmeyer, M. Leo, *Helv. Chim. Acta* **1932**, *15*, 1171.
[2] N. Brown, *Bioisosteres in Medicinal Chemistry*, Wiley-VCH, Weinheim, Germany, **2012**.
[3] a) A. Burger, *Prog. Drug Res.* **1991**, *37*, 288; b) G. A. Patani, E. J. LaVoie, *Chem. Rev.* **1996**, *96*, 3147; c) P. H. Olsen, *Curr. Opin. Drug Discovery Dev.*

2001, *4*, 471; d) L. M. Lima, E. J. Barriero, *Curr. Med. Chem.* **2005**, *12*, 23; e) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529.
[4] L. Peterlin-Masic, D. Kikelj, *Tetrahedron* **2001**, *57*, 7073.
[5] a) T. Lu, T. Markotan, F. Coppo, B. Tomczuk, C. Crysler, S. Eisennagel, J. Spurlino, L. Gremminger, R. M. Soll, E. C. Giardino, R. Bone, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3727; b) R. M. Soll, T. Lu, B. Tomczuk, C. R. Illig, C. Fedde, S. Eisennagel, R. Bone, L. Murphy, J. Spurlino, F. R. Salemme, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1; c) P. Ghorai, A. Kraus, M. Keller, C. Gotte, P. Igel, E. Schneider, D. Schnell, G. Bernhardt, S. Dove, M. Zabel, S. Elz, R. Seifert, A. Buschauer, *J. Med. Chem.* **2008**, *51*, 7193; d) C.-W. Lee, H. Cao, K. Ichiyama, T. M. Rana, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4243.
[6] a) F. Saczewski, L. Balewski, *Expert Opin. Ther. Pat.* **2009**, *19*, 1417; b) F. Saczewski, L. Balewski, *Expert Opin. Ther. Pat.* **2013**, *23*, 965.
[7] a) L. Heys, C. G. Moore, P. J. Murphy, *Chem. Soc. Rev.* **2000**, *29*, 57; b) R. G. S. Berlinck, A. E. Trindade-Silva, M. F. C. Santos, *Nat. Prod. Rep.* **2012**, *29*, 1382.
[8] S. S. Ebada, P. Proksch, *Mini-Rev. Med. Chem.* **2011**, *11*, 225.
[9] a) J.-M. Tinti, C. Nofre, "Design of Sweeteners" in *Sweeteners: Discovery, Molecular Design and Chemoreseption* (Eds.: D. E. Walters, F. T. Orthoefer, G. E. DuBois), ACS, Washington, DC, USA, **1991**, pp. 88–112; b) S. Nagarajan, M. S. Kellogg, G. E. DuBois, G. Hellekant, *J. Med. Chem.* **1996**, *39*, 4167; c) D. Glaser, *Pure Appl. Chem.* **2002**, *74*, 1153.
[10] See: T. Güthner, B. Mertschenk, B. Schulz, "Guanidine and Derivatives" in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, Germany, **2012**, vol. 17, pp. 175–189.
[11] The "deltic" terminology follows that introduced by West for 2,3-dihydroxycyclopropenone or "deltic acid", which is a macrostere of carbonic acid: a) D. Eggerding, R. West, *J. Am. Chem. Soc.* **1975**, *97*, 207; b) D. Eggerding, R. West, *J. Am. Chem. Soc.* **1976**, *98*, 3641.
[12] K. Komatsu, T. Kitagawa, *Chem. Rev.* **2003**, *103*, 1371.
[13] J. S. Bandar, T. H. Lambert, *Synthesis* **2013**, *45*, 2485.
[14] The only reported TAC with more than one N–H function was 1,2,3-trianilinocyclopropenium chloride, which was described as a "nitrogen analogue of deltic acid". We have not found this procedure to be generalizable: a) R. Weiss, M. Hertel, *J. Chem. Soc., Chem. Commun.* **1980**, 223. Recently, a TAC was reported with a single NH_2 function: b) O. J. Curnow, M. T. Holmes, L. C. Ratten, K. J. Walst, R. Yunis, *RSC Adv.* **2012**, *2*, 10794.
[15] a) Z. Yoshida, Y. Tawara, *J. Am. Chem. Soc.* **1971**, *93*, 2573; b) C. Wilcox, R. Breslow, *Tetrahedron Lett.* **1980**, *21*, 3241.
[16] Deprotection of the DMB group with TFA produces a calix[4]arene, which can typically be easily removed by filtration: a) O. M. Falana, E. Al-Farhan, P. M. Keehn, R. Stevenson, *Tetrahedron Lett.* **1994**, *35*, 65; b) Y. Sawama, M. Masuda, S. Asai, R. Goto, S. Nagata, S. Nishimura, Y. Monguchi, H. Sajiki, *Org. Lett.* **2015**, *17*, 434.
[17] D. Athanassiadis, W. I. Cranston, B. E. Juel-Jensen, D. O. Oliver, *Br. Med. J.* **1966**, *2*, 732.
[18] H. Harada, H. Miyake, K. Ochi, J. Tanaka, I. Kimura, *Int. J. Pancreatol.* **1991**, *9*, 75.
[19] C. G. Östenson, *Exp. Clin. Endocrinol.* **1983**, *81*, 255.
[20] a) W. Raasch, U. Schäfer, J. Chun, P. Dominiak, *Br. J. Pharmacol.* **2001**, *133*, 755; b) H. A. Plietz, *CNS Drugs* **2007**, *21*, 885.
[21] T. J. Baker, N. W. Luedtke, Y. Tor, M. Goodman, *J. Org. Chem.* **2000**, *65*, 9054.
[22] Z. Yoshida, Y. Tawara, S. Hirota, H. Ogoshi, *Bull. Chem. Soc. Jpn.* **1974**, *47*, 797.
[23] J. R. Butchard, O. J. Curnow, R. J. Pipal, W. T. Robinson, R. Shang, *J. Phys. Org. Chem.* **2008**, *21*, 127.
[24] a) H. Yamakoshi, K. Dodo, M. Okada, J. Ando, A. Palonpon, K. Fujita, S. Kawata, M. Sodeoka, *J. Am. Chem. Soc.* **2011**, *133*, 6102; b) L. Wei, Y. Yu, Y. Shen, W. C. Wang, W. Min, *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 11226; c) L. Wei, F. Hu, Y. Shen, Z. Chen, Y. Yu, C. Lin, M. C. Wang, W. Min, *Nature Methods* **2014**, *11*, 410.
[25] a) P. A. Wender, D. J. Mitchell, K. Pattabiraman, E. T. Pelkey, L. Steinman, J. B. Rothbard, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 13003; b) S. Futaki, T. Suzuki, W. Ohashi, T. Yagami, S. Tanaka, K. Ueda, Y. Sugiura, *J. Biol. Chem.* **2001**, *276*, 5836; c) E. G. Stanzl, B. M. Trantow, J. R. Vargas, P. A. Wender, *Acc. Chem. Res.* **2013**, *46*, 2944; d) C. V. Bonduelle, E. R. Gillies, *Pharmaceuticals* **2010**, *3*, 636.
[26] a) J. B. Rothbard, T. C. Jessop, R. S. Lewis, B. A. Murray, P. A. Wender, *J. Am. Chem. Soc.* **2004**, *126*, 9506; b) P. A. Wender, W. C. Galliher, E. A. Goun, L. R. Jones, T. H. Pillow, *Adv. Drug Delivery Rev.* **2008**, *60*, 452.
[27] H. H. Chung, G. Harms, C. M. Seong, B. H. Choi, C. Min, J. P. Taulane, M. Goodman, *Biopolymers* **2004**, *76*, 83.

Received: February 8, 2016
Published Online: March 14, 2016

