Heterocycles

DOI: 10.1002/anie.201106024

Skeletal Fusion of Small Heterocycles with Amphoteric Molecules**

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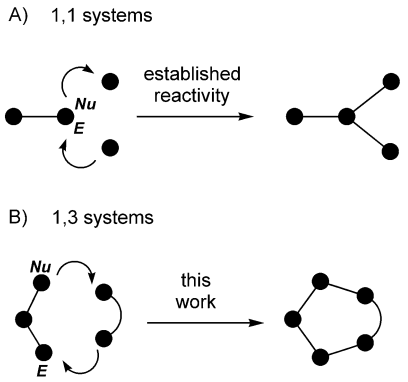
Small heterocycles provide the core structure of a vast range of modern pharmaceuticals. The so-called privileged motifs have been the engine of drug discovery and molecular probe development.[1] During a discovery campaign, functional groups designed to interact with biological targets of interest are commonly built off electrophilic sites on the heterocyclic scaffolds. Despite the commercial availability of a wide range of nucleophilic reagents, this general strategy has a significant shortcoming: introduction of an electrophilic handle such as an acrylate, an epoxide, or an aziridine[2] often requires methods with low functional group tolerance, which limits the effectiveness of late-stage, diversity-oriented approaches.[3,4] Amphoteric aziridine aldehydes, developed in our laboratory, facilitate chemoselective transformations and can circumvent protecting-group manipulations.[5] These molecules have led us to consider processes that are characterized by high bond-forming efficiency[6] and result in rapid synthesis of privileged heterocyclic frameworks by "skeletal fusion". The method presented here demonstrates how we have reached this goal by preparing and elaborating medicinally important templates that can be employed for the presentation of *cis*-amide bonds.[7] Our method of fusing small heterocycles should facilitate diversity-oriented synthesis of other stereochemically rich motifs.

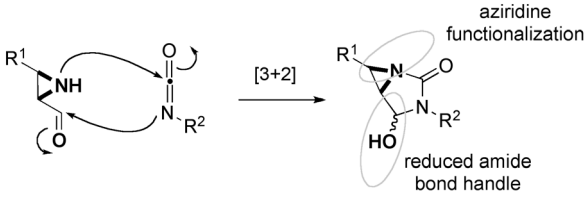
Isocyanides, first synthesized in 1859, are the best known amphoteric reagents. Two of the most widely used multicomponent reactions, the Passerini reaction and the Ugi four-component condensation,[8] owe their efficiency to the amphoteric nature of the isocyanide's terminal carbon. Isocyanides are (1,1) amphoteric molecules because the α-carbon center can establish a connection with both nucleophile and electrophile (for a conceptual representation, see Scheme 1 A). Our continuing efforts to expand the scope of synthetically useful amphoteric molecules have led us to examine systems in which the electrophilic and nucleophilic nodes of reactivity are separated by one or more atoms. Of particular interest are (1,3) systems exemplified by the unprotected α-amino aldehydes in which NH aziridine, a well-established precursor to complex amines, plays a pivotal role.[4] We recently initiated a search for two-atom π-electrophilic reaction partners for amphoteric aziridine aldehydes.



Scheme 1. Examples of connectivity in amphoteric molecule-induced transformations.

The goal was to build a bridge between the "Nu" and "E" nodes, resulting in a net [3+2] annulation (Scheme 1 B). To the best of our knowledge, no such reactions of amphoteric molecules have been reported.

We envisioned that aziridine aldehydes would act as three-atom "connectors", engaging the π-system of isocyanates in a [3+2] fashion. This fusion was projected to supply a hydantoin scaffold equipped with a strategically placed reduced imide bond and an electrophilic aziridine functionality suitable for further chemical modifications (Scheme 2).



Scheme 2. Construction of the reduced-hydantoin scaffold by using aziridine aldehydes.

Hydantoins are well represented in the structures of natural products and synthetic bioactive compounds. Examples of therapeutic agents containing the hydanoin core include phosphenytoin, phenytoin, and ethotoin, to name a few. The rigid and planar hydantoin group provides an excellent means of presenting *cis*-amide bond conformers. This feature is the main reason for sustained interest in this small heterocycle. For instance, spirohydantion undergoes little loss of conformational energy on binding to glycogen phosphorylase glucopyranose.[9] The *cis*-amide group of spirohydantoin is the determinant of both specificity and affinity by virtue of hydrogen bonding to the protein core. Common methods of

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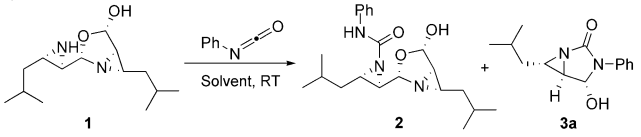
[**] The authors thank the Natural Science and Engineering Research Council (NSERC) and the Canadian Institutes of Health Research (CIHR) for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201106024.

making hydantoins include the Bucherer–Bergs reaction,[10a–c] the Read method,[10d] and methods using ureas and dicarbonyl compounds.[11,12] A particularly significant goal is to develop approaches that would allow for late-stage structural modification of the hydantoin scaffold.

When aziridine aldehyde dimer **1** was exposed to phenyl isocyanate in diethyl ether, compound **2** was obtained in quantitative yield as a result of simple addition of the aziridine aldehyde dimer on to the C=N bond of the isocyanate (Table 1, entry 1). 2,2,2-Trifluoroethanol (TFE)

Table 1: Optimization of reduced hydantoin synthesis with mixed solvent systems.[a]



Entry	% Et_2O	% HFIP	% H_2O	Product ratio (**2**:**3a**)[b]	Combined product yield [%][c]
1	100	0	0	100:0	quantitative
2	0	100	0	27:73	56
3	0	90	10	16:84	81
4	0	80	20	0:100	85
5	0	70	30	0:100	80
6	0	60	40	0:100	63
7	0	50	50	0:100	55

[a] Reactions were performed at room temperature by using 1.0 equiv aziridine aldehyde and 1.5 equiv isocyanate. [b] Product ratio was determined by analysis of crude reaction mixtures by ^{1}H NMR spectroscopy. [c] Yields of isolated products.

and 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) promote aziridine aldehyde dimer dissociation by disrupting the intramolecular hydrogen bond that exists between the NH aziridine and the OH of the hemiacetal.[5a,c,d,f,13] HFIP was thus tested in the reaction between aziridine aldehyde dimer **1** and phenyl isocyanate. Gratifyingly, besides a small amount of the dimeric by-product **2**, the reduced hydantoin **3a** posessing the urea motif equipped with three contiguous stereocenters was obtained as the major product (Table 1, entry 2). X-ray crystallography confirmed the structure of **3a**.[14] The crystal structure revealed the severe strain resulting in the C–H bond of the hemiaminal adopting a nearly orthogonal (dihedral angle: 94°) orientation with regard to the adjacent C–H bond on the aziridine ring (Figure 1). This feature was also supported by the lack of coupling between the two protons. The aziridine amide portion of the molecule is tilted with respect to the carbonyl plane, which is evident in the elongated C–N bond (1.420 Å) of the aziridine amide, compared to a typical C–N bond (1.380 Å) of regular amides.

Further optimization of the reaction conditions revealed that addition of water to HFIP caused an increase in the production of reduced hydantoin **3a** (Table 1, entries 2–7). This observation could be attributed to the generation of a more polar protic medium, which would further promote the dissociation of the dimeric aziridine aldehyde. The optimal yield and selectivity were reached by using the solvent system

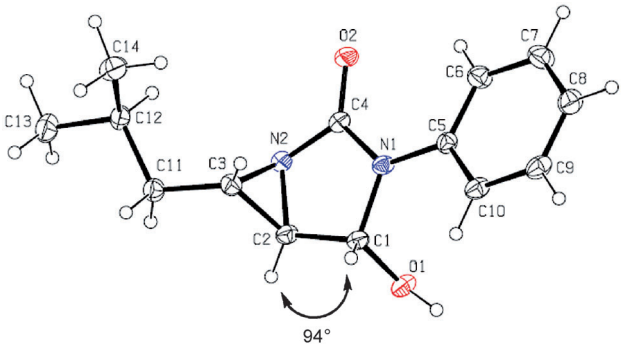
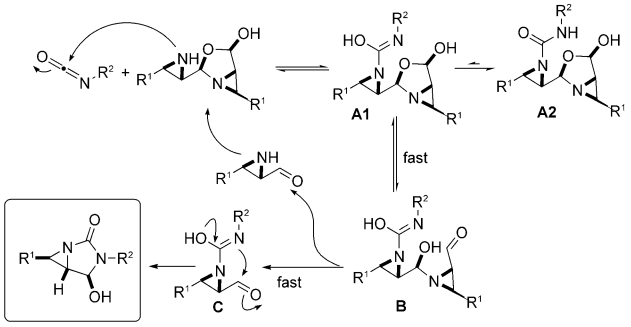


Figure 1. X-ray structure of **3a**.

of 8:2 HFIP:H_2O (v/v) (Table 1, entry 4). Additional water resulted in a decreased product yield (Table 1, entries 5–7), possibly due to the production of acyclic urea by-products.

The observation of **2** has given us additional insight into the mechanism of the reduced hydantoin product formation. Subjecting pure **2** to the optimized solvent system (8:2 HFIP:H_2O) yielded final product **3a** plus the starting material **1**. This observation supports a proposed reaction pathway operating through the mechanism shown in Scheme 3. Following the initial nucleophilic attack of the aziridine



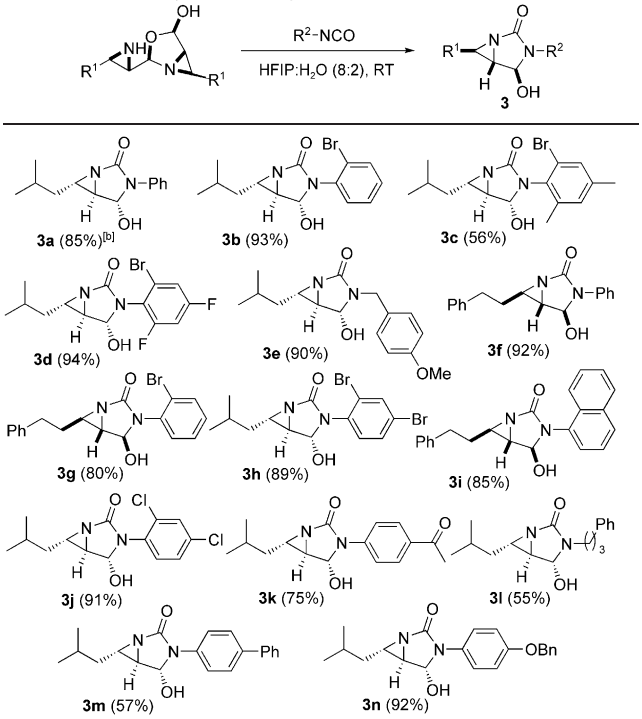
Scheme 3. Proposed mechanism for reduced hydantoin formation.

aldehyde dimer onto the isocyanate, the dimeric intermediate **A1**/**A2** rapidly collapses to generate the monomeric adduct **B**, which proceeds to a 5-(enol-*endo*)-*exo*-trig cyclization to afford the aziridine-fused five-membered heterocycle. The monomeric aziridine aldehyde released from the intermediate re-dimerizes and re-enters the reaction.

In order to test the generality of this new synthesis, a number of reduced hydantoins were made using the HFIP:H_2O (8:2, v/v) solvent system (Table 2). Yields are good to excellent, with high levels of diastereoselectivity. In all cases the product is isolated as a solid material that can be readily purified by trituration with hexanes/acetone. The commercial availability of aziridine aldehydes and isocyanates should facilitate convergent library synthesis.

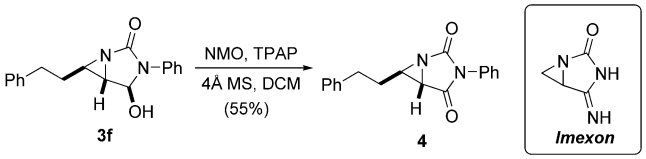
Reduced hydantoins represent excellent starting points for further transformations.[15] In one application, oxidation of the hemiaminal moiety revealed a new class of heterocylic scaffolds equipped with the structural features present in the

Table 2: Reduced hydantoin scope.[a]



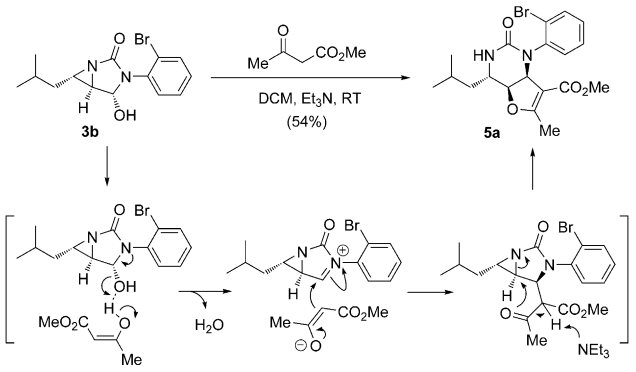
[a] Reactions were performed at room temperature by using 1.0 equiv aziridine aldehyde and 1.5 equiv isocyanate in HFIP:H_2O (8:2, v/v). [b] All values in parentheses represent yields of isolated products.

anti-cancer agent Imexon.[16] Thus, subjecting compound **3 f** to the mild oxidation with TPAP/NMO, a novel aziridine-fused hydantoin derivative **4** was isolated (Scheme 4). Importantly, the strained aziridine functionality remained intact during this transformation. Imexon-type scaffolds are used in the treatment of various types of cancer including breast, pancreatic, lung, and prostate.[17] Inspired by Imexon, compounds such as **4** can open up new opportunities in the design of DNA alkylating agents.



Scheme 4. Oxidation of aziridine fused reduced hydantoin **3 f**.

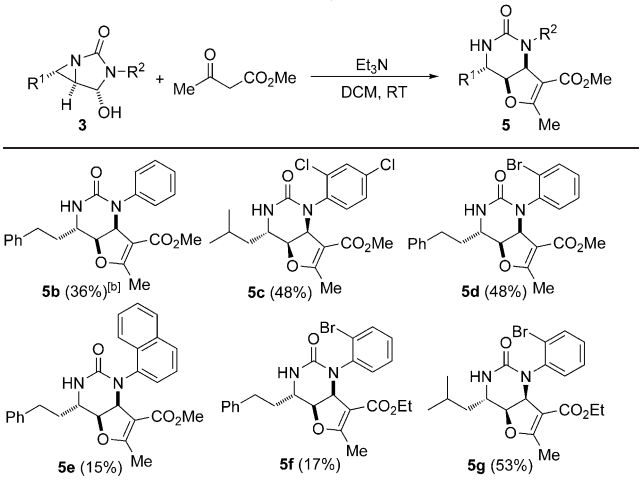
With the strategically placed reduced imide bond in hand, we opted to evaluate if other kinds of reactivity could be accessed through the intermediacy of iminium ions. When the reduced hydantoin **3b** was exposed to methyl acetoacetate in the presence of Et_3N, a six-membered urea **5a** fused with the dihydrofuran ring was isolated (Scheme 5). The reaction mechanism likely operates by acetoacetate substituting the hydroxy group at the hemiaminal carbon followed by a nucleophilic ring-opening of the aziridine ring with the nascent enol functionality. A variety of novel dihydrofuran-fused cyclic ureas were subsequently obtained (Table 3).



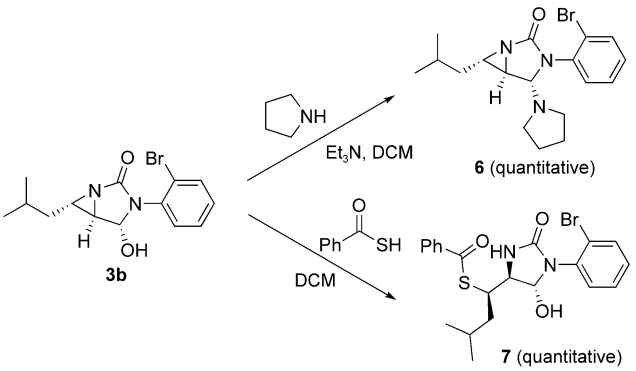
Scheme 5. The reaction between **3 b** and methyl acetoacetate.

The reduced hydantoins showed nucleophile-dependent reactivity (Scheme 6). Pyrrolidine displaced the hydroxy group of compound **3b** in DCM, affording **6** in quantitative yield and leaving the aziridine ring intact. When exposed to thiobenzoic acid, which is a softer nucleophile, **3a** was converted to reduced hydantoin **7** by the aziridine ring

Table 3: Formation of fused urea dihydrofurans.[a]



[a] Reactions were performed at room temperature by using 1.0 equiv reduced hydantoin, 1.5 equiv β-ketoester, and 2.0 equiv Et_3N in DCM. [b] All values in parentheses represent yields of isolated products.



Scheme 6. Site-specific reactivity of the reduced hydantoins with nucleophiles.

scission that did not interfere with the hemiaminal functionality.

In summary, we have shown that (1,3) amphoteric molecules, exemplified by aziridine aldehydes, partake in highly efficient annulations with readily accessible isocyanates. Our [3+2] chemistry delivered a new class of aziridine-fused hydantoin derivatives equipped with three contiguous stereocenters. A reduced imide bond was installed in the course of the annulation, providing a strategic handle for subsequent skeletal transformations that delivered small, stereochemically rich heterocycles capable of presenting *cis*-amide bonds in different structural contexts. Downstream modifications of this hydantoin platform resulted in a series of new heterocycles including dihydrofuran-fused cyclic ureas and aziridine-fused hydantoins (Imexon analogues). Given the availability of two-atom π-electrophilic building blocks, such as aldehydes, imines, ketenes, carbodiimides, carbon dioxide, carbon disulfide, to name a few, we expect that [3+2] annulations involving amphoteric aziridine aldehydes can open up extensive opportunities for the construction of novel heterocyclic frameworks for use in chemical biology, catalysis, and other endeavors. The reported reactivity may also form a foundation for new multicomponent reactions.

Experimental Section

General procedure for the synthesis of reduced hydantoin **3**: The aziridine aldehyde dimer (0.079 mmol, 1.0 equiv) was charged into a vial equipped with a stir bar. A minimal volume (0.4 mL) of 8:2 HFIP:H_2O (v/v) was added to dissolve the aziridine aldehyde dimer. The isocyanate (0.119 mmol, 1.5 equiv) was added to the resulting solution and the contents of the vial were allowed to stir at room temperature for 45–60 min. CH_2Cl_2 (2 mL) and water (2 mL) were added. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (2 mL × 2). The organic layers were combined, dried with magnesium sulfate, filtered, and concentrated. The crude material solidified upon concentration under vacuum and was purified by triturating with a mixture of hexanes and acetone (variable solvent ratio depending on the product). The solvent was decanted and the collected solid product was allowed to dry under an open atmosphere.

Received: August 25, 2011
Published online: October 11, 2011

Keywords: amino aldehydes · amphoteric molecule · chemoselectivity · hydantoin · regioselectivity

[1] a) M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347 – 361; b) S. V. Frye, *Nat. Chem. Biol.* **2010**, *6*, 159 – 161.

[2] *Aziridines and Epoxides in Organic Synthesis* (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2006**.

[3] For reviews in diversity-oriented synthesis, see: a) T. E. Nielsen, S. L. Schreiber, *Angew. Chem.* **2008**, *120*, 52 – 61; *Angew. Chem. Int. Ed.* **2008**, *47*, 48 – 56; b) K. Hübel, T. Leßmann, H. Waldmann, *Chem. Soc. Rev.* **2008**, *37*, 1361 – 1374; c) M. D. Burke, S. L. Schreiber, *Angew. Chem.* **2004**, *116*, 48 – 60; *Angew. Chem. Int. Ed.* **2004**, *43*, 46 – 58; d) S. L. Schreiber, *Science* **2000**, *287*, 1964 – 1969.

[4] For recent examples of diversity-oriented synthesis of heterocycles, see: a) J. Barjau, G. Schnakenburg, S. R. Waldvogel, *Angew. Chem.* **2011**, *123*, 1451 – 1455; *Angew. Chem. Int. Ed.* **2011**, *50*, 1415 – 1419; b) M. R. Bhandari, M. Yousufuddin, C. J. Lovely, *Org. Lett.* **2011**, *13*, 1382 – 1385; c) D. S. Ermolat'ev, J. B. Bariwal, H. P. L. Steenackers, S. C. De Keersmaecker, E. V. Van der Eycken, *Angew. Chem.* **2010**, *122*, 9655 – 9658; *Angew. Chem. Int. Ed.* **2010**, *49*, 9465 – 9468; d) D. Pizzirani, T. Kaya, P. A. Clemons, S. L. Schreiber, *Org. Lett.* **2010**, *12*, 2822 – 2825; e) E. Airiau, N. Girard, A. Mann, J. Salvadori, M. Taddei, *Org. Lett.* **2009**, *11*, 5314 – 5317; f) J. D. Sunderhaus, S. F. Martin, *Chem. Eur. J.* **2009**, *15*, 1300 – 1308; g) B. A. Arndtsen, *Chem. Eur. J.* **2009**, *15*, 302 – 313; h) W. R. J. D. Galloway, A. Bender, M. Welch, D. R. Spring, *Chem. Commun.* **2009**, 2446 – 2462; i) G. L. Thomas, R. J. Spandl, F. G. Glansdorp, M. Welch, A. Bender, J. Cockfield, J. A. Lindsay, C. Bryant, D. F. J. Brown, O. Loiseleur, H. Rudyk, M. Ladlow, D. R. Spring, *Angew. Chem.* **2008**, *120*, 2850 – 2854; *Angew. Chem. Int. Ed.* **2008**, *47*, 2808 – 2812; j) E. E. Wyatt, W. R. J. D. Galloway, G. L. Thomas, M. Welch, O. Loiseleur, A. T. Plowright, D. R. Spring, *Chem. Commun.* **2008**, 4962 – 4964; k) D. García-Cuadrado, S. Barluenga, N. Winssinger, *Chem. Commun.* **2008**, 4619 – 4621; l) H. An, S.-J. Eum, M. Koh, S. K. Lee, S. B. Park, *J. Org. Chem.* **2008**, *73*, 1752 – 1761; m) M. Scheck, M. A. Koch, H. Waldmann, *Tetrahedron* **2008**, *64*, 4792 – 4802; n) N. Isambert, R. Lavilla, *Chem. Eur. J.* **2008**, *14*, 8444 – 8454; o) J. D. Sunderhaus, C. Dockendorff, S. F. Martin, *Org. Lett.* **2007**, *9*, 4223 – 4226; p) D. Tejedor, A. Sántos-Expósito, F. García-Tellado, *Chem. Eur. J.* **2007**, *13*, 1201 – 1209; q) S. K. Ko, H. J. Jang, E. Kim, S. B. Park, *Chem. Commun.* **2006**, 2962 – 2964; r) D. J. Vugts, M. M. Koningstein, R. F. Schmitz, F. J. J. de Kanter, M. B. Groen, R. V. A. Orru, *Chem. Eur. J.* **2006**, *12*, 7178 – 7189; s) O. Jiménez, G. de La Rosa, R. Lavilla, *Angew. Chem.* **2005**, *117*, 6679 – 6683; *Angew. Chem. Int. Ed.* **2005**, *44*, 6521 – 6525; t) L. A. Wessjohann, B. Voigt, D. G. Rivera, *Angew. Chem.* **2005**, *117*, 4863 – 4868; *Angew. Chem. Int. Ed.* **2005**, *44*, 4785 – 4790; u) V. Sharma, J. J. Tepe, *Org. Lett.* **2005**, *7*, 5091 – 5094; v) J. A. González-Vera, M. T. García-López, R. Herranz, *J. Org. Chem.* **2005**, *70*, 3660 – 3666; w) X. Lei, N. Zaarur, M. Y. Sherman, J. A. Porco, Jr., *J. Org. Chem.* **2005**, *70*, 6474 – 6483; x) D. Tejedor, D. González-Cruz, A. Sántos-Expósito, J. J. Marrero-Tellado, P. de Armas, F. García-Tellado, *Chem. Eur. J.* **2005**, *11*, 3502 – 3510; y) S. J. Taylor, A. M. Taylor, S. L. Schreiber, *Angew. Chem.* **2004**, *116*, 1713 – 1717; *Angew. Chem. Int. Ed.* **2004**, *43*, 1681 – 1685; z) M. D. Burke, E. M. Berger, S. L. Schreiber, *J. Am. Chem. Soc.* **2004**, *126*, 14095 – 14104. aa) D. Tejedor, S. López-Tosco, J. González-Platas, F. García-Tellado, *Chem. Eur. J.* **2009**, *15*, 838 – 842; ab) D. Tejedor, G. Méndez-Abt, F. García-Tellado, *Chem. Eur. J.* **2010**, *16*, 428 – 431; ac) D. Tejedor, S. López-Tosco, J. González-Platas, F. García-Tellado, *Chem. Eur. J.* **2010**, *16*, 3276 – 3280.

[5] a) R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2006**, *128*, 14772 – 14773; b) R. Hili, A. K. Yudin, *Angew. Chem.* **2008**, *120*, 4256 – 4259; *Angew. Chem. Int. Ed.* **2008**, *47*, 4188 – 44191; c) R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2009**, *131*, 16404 – 16406; d) R. Hili, V. Rai, A. K. Yudin, *J. Am. Chem. Soc.* **2010**, *132*, 2889 – 2891; e) B. H. Rotstein, V. Rai, R. Hili, A. K. Yudin, *Nat. Protoc.* **2010**, *5*, 1813 – 1822; f) S. Baktharaman, N. A. Afagh, A. Vandersteen, A. K. Yudin, *Org. Lett.* **2010**, *12*, 240 – 243; g) N. Assem, A. Natarajan, A. K. Yudin, *J. Am. Chem. Soc.* **2010**, *132*, 10986 – 10987; h) Z. He, A. K. Yudin, *Angew. Chem.* **2010**, *122*, 1651 – 1654; *Angew. Chem. Int. Ed.* **2010**, *49*, 1607 – 1610.

[6] L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115 – 136.

[7] M. Meusel, M. Gütschow, *Org. Prep. Proced. Int.* **2004**, *36*, 391 – 443.

[8] A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300 – 3344; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168 – 3210.

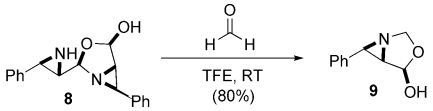
[9] M. Gregoriou, M. E. M. Noble, K. A. Watson, E. F. Garman, T. M. Krulle, C. De La Fuente, G. W. J. Fleet, N. G. Oikonomakos, L. N. Johnson, *Protein Sci.* **1998**, *7*, 915 – 927.

[10] a) H. Bergs, Ger. Pat. 566,094, **1929**; b) H. T. Bucherer, W. Steiner, *J. Prakt. Chem.* **1934**, *140*, 291 – 316; c) E. Ware, *Chem. Rev.* **1950**, *46*, 403 – 470; d) W. T. Read, *J. Am. Chem. Soc.* **1922**, *44*, 1746 – 1749.

[11] a) G. G. Muccioli, J. H. Poupaert, J. Wouters, B. Norberg, W. Poppitz, G. K. E. Scriba, D. M. Lambert, *Tetrahedron* **2003**, *59*, 1301 – 1307; b) G. G. Muccioli, J. Wouters, J. H. Poupaert, B. Norberg, W. Poppitz, G. K. E. Scriba, D. M. Lambert, *Org. Lett.* **2003**, *5*, 3599 – 3602.

[12] For recent examples of hydantoin synthesis, see: a) T. Miura, Y. Mikano, M. Murakami, *Org. Lett.* **2011**, *13*, 3560 – 3563; b) O. A. Attanasi, L. De Crescentini, G. Favi, S. Nicolini, F. R. Perrulli, S. Santeusanio, *Org. Lett.* **2011**, *13*, 353 – 355; c) G. Baccolini, C. Boga, C. Delpivo, G. Micheletti, *Tetrahedron Lett.* **2011**, *52*, 1713 – 1717; d) M. Gao, Y. Yang, Y.-D. Wu, C. Deng, W.-M. Shu, D.-X. Zhang, L.-P. Cao, N.-F. She, A.-X. Wu, *Org. Lett.* **2010**, *12*, 4026 – 4029; e) F. Olimpieri, M. C. Bellucci, A. Volonterio, M. Zanda, *Eur. J. Org. Chem.* **2009**, 6179 – 6188; f) S. M. Dumbris, D. J. Díaz, L. McElwee-White, *J. Org. Chem.* **2009**, *74*, 8862 – 8865; g) B. Zhao, H. Du, Y. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 7220 – 7221; h) V. Kumar, M. P. Kaushik, A. Mazumdar, *Eur. J. Org. Chem.* **2008**, 1910 – 1916; i) Y. Kuninobu, K. Kikuchi, K. Takai, *Chem. Lett.* **2008**, *37*, 740 – 741; j) A. Alizadeh, E. Sheikhi, *Tetrahedron Lett.* **2007**, *48*, 4887 – 4890; k) N. Dieltiens, D. D. Claeys, V. V. Zhdankin, V. N. Nemykin, B. Allaert, F. Verpoort, C. V. Stevens, *Eur. J. Org. Chem.* **2006**, 2649 – 2660; l) C. Montagne, J. J. Shiers, M. Shipman, *Tetrahedron Lett.* **2006**, *47*, 9207 – 9209; m) B. A. Bhat, K. L. Dhar, S. C. Puri, M. Spiteller, *Synlett* **2006**, 2723 – 2726; n) J. M. Ignacio, S. Macho, S. Marcaccini, R. Pepino, T. Torroba, *Synlett* **2005**, 3051 – 3054; o) A. Alizadeh, H. R. Bijanzadeh, *Synthesis* **2004**, 3023 – 3028; p) V. Wehner, H.-U. Stilz, S. N. Osipov, A. S. Golubev, J. Sieler, K. Burger, *Tetrahedron* **2004**, *60*, 4295 – 4302; q) M. Meusel, A. Ambrozak, T. K. Hecker, M. Gütschow, *J. Org. Chem.* **2003**, *68*, 4684 – 4692; r) C. Hulme, L. Ma, J. J. Romano, G. Morton, S.-Y. Tang, M.-P. Cherrier, S. Choi, J. Salvino, R. Labaudiniere, *Tetrahedron Lett.* **2000**, *41*, 1889 – 1893; s) S. Najdi, K.-H. Park, M. M Olmstead, M. J. Kurth, *Tetrahedron Lett.* **1998**, *39*, 1685 – 1688; t) K.-H. Park, M. M Olmstead, M. J. Kurth, *J. Org. Chem.* **1998**, *63*, 113 – 117.

[13] An unpublished study by our group revealed that an aziridine-fused cyclic hemiacetal **9** can be generated in a similar [3+2] reaction between the aziridine aldehyde dimer **8** and formaldehyde in TFE.



[14] See Supporting Information.

[15] For recent examples of synthetic applications involving reduced hydantoins, see: a) J. L. Methot, T. A. Dunstan, D. M. Mampreian, B. Adams, M. D. Altman, *Tetrahedron Lett.* **2008**, *49*, 1155 – 1159; b) T. A. Cernak, J. L. Gleason, *J. Org. Chem.* **2008**, *73*, 102 – 110; c) L. Tang, D. Romo, *Heterocycles* **2007**, *74*, 999 – 1008; d) A. Pesquet, A. Daïch, L. Van Hijfte, *J. Org. Chem.* **2006**, *71*, 5303 – 5311; e) S. P. Chavan, A. G. Chittiboyina, G. Ramakrishna, R. B. Tejwani, T. Ravindranathan, S. K. Kamat, B. Rai, L. Sivadasan, K. Balakrishnan, S. Ramalingam, V. H. Deshpande, *Tetrahedron* **2005**, *61*, 9273 – 9280; f) J. A. Parihar, M. M. V. Ramana, *Tetrahedron Lett.* **2003**, *44*, 1843 – 1845; g) E. J. Corey, M. M. Mehrotra, *Tetrahedron Lett.* **1988**, *29*, 57 – 60.

[16] B. S. Iyengar, R. T. Dorr, W. A. Remers, *J. Med. Chem.* **2004**, *47*, 218 – 223.

[17] S. Moulder, N. Dhillon, C. Ng, D. Hong, J. Wheler, A. Naing, S. Tse, A. L. Paglia, R. Dorr, E. Hersh, M. Boytim, R. Kurzrock, *Invest. New Drugs* **2010**, *28*, 634 – 640.

