Synthesis of Axinohydantoins

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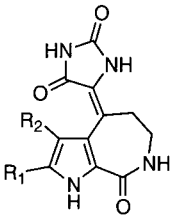
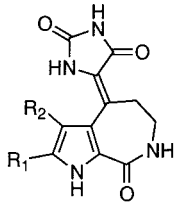
A short synthesis of the hydantoin-containing marine sponge metabolites axinohydantoins is described. A key feature of the synthesis is a putative biomimetic, intramolecular cyclization of α-functionalized imidazolone **5**, which affords the tricyclic pyrroloazepinone framework comprising **6**. In addition, the conversion of imidazolones to α,*β*-unsaturated hydantoins is outlined and represents a new approach to these heterocyclic systems.

Over the last two decades, a series of tricyclic pyrrole natural products have been isolated from various genera of marine sponges.[1] Each share in common a fused bicyclic pyrrolo[2,3-*c*]azepine core to which either a 2-aminoimidazole, glycocyamidine, or hydantoin unit is appended. In 1990, Pettit and co-workers[2] isolated (*E*)-axinohydantoin (**1a**) from the sponge *Axinella*, and its structure was determined by X-ray crystallography. Subsequently, the isolation of (*Z*)-axinohydantoin (**2a**) and (*Z*)-debromoaxinohydantoin (**2b**) from *Stylotella aurantium* and *Hymeniacidon* sp., respectively, has been reported by two groups.[3] Axinohydantoins have been shown to inhibit protein kinase C.[3a]

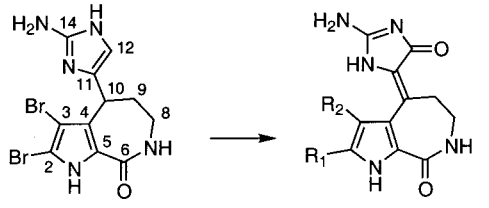


(*E*)-axinohydantoin (**1a**) R_1=Br, R_2=H
(*E*)-debromoaxinohydantoin (**1b**) R_1=R_2=H
(*E*)-bromoaxinohydantoin (**1c**) R_1=R_2=Br

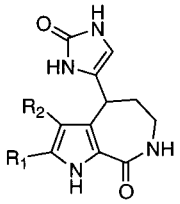


(*Z*)-axinohydantoin (**2a**) R_1=Br, R_2=H
(*Z*)-debromoaxinohydantoin (**2b**) R_1=R_2=H
(*Z*)-bromoaxinohydantoin (**2c**) R_1=R_2=Br

The hydantoin-containing axinohydantoins are structurally related to hymenialdisines which contain a glycocyamidine unit.[4] In previous work from this lab,[5] the synthesis and stereoselective conversion of hymenin[6] to (*Z*)-hymenialdisines was reported (eq 1). Formation of the thermodynamically less stable (*E*)-isomer was not observed. In the present study, a similar approach for installing the hydantoin unit of axinohydantoins **1** and **2** was envisioned from hymenin analogues **6**. The problem of accessing the hydantoin nucleus from an imidazolone precursor as well as forming the less thermodynamically stable (*E*)-axinohydantoins by this approach remained an open question. Herein, we report the first syntheses of (*E*)- and (*Z*)-debromoaxinohydantoins **1b** and **2b** and (*E*)-and (*Z*)-bromoaxinohydantoins **1c** and **2c**.



hymenin (*Z*)-hymenialdisines R_1=R_2=H or Br (eq 1)



6: R_1=R_2=H or Br

The biosynthetic pathway to axinohydantoins is unknown but plausible pathways may involve linear precursors such as α-functionalized imidazolones **5**. An

(1) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1−49 and references therein.

(2) Pettit, G. R.; Herald, C. L.; Leet, J. E.; Gupta, R.; Schaufelberger, D. E.; Bates, R. B.; Clewlow, P. J.; Doubek, D. L.; Manfredi, K. P.; Rützler, K.; Schmidt, J. M.; Tackett, L. P.; Ward, F. B.; Bruck, M.; Camou, F. *Can. J. Chem*. **1990**, *68*, 1621−1624.

(3) (a) Patil, A. D.; Freyer, A. J.; Killmer, L.; Hofmann, G.; Johnson, R. K. *Nat. Prod. Lett.* **1997**, *9*, 201−207. (b) Inaba, K.; Sato, H.; Tsuda, M.; Kobayashi, J. *J. Nat. Prod.* **1998**, *61*, 693−695. Although axinohydantoins were subsequently referred to as spongiacidins, we opted to use the name originally given as axinohydantoins.

(4) (a) Sharma, G. M.; Buyer, J. S.; Pomerantz, M. W. *J. Chem. Soc., Chem. Commun*. **1980**, 435−436. (b) Cimino, G.; DeRosa, S.; DeStefano, S.; Mazzarella, L.; Puliti, R.; Sodano, G. *Tetrahedron Lett.* **1982**, *23*, 767−768. (c) Kitagawa, I.; Kobayashi, M.; Kitanaka, K.; Kido, M.; Kyogoku, Y. *Chem. Pharm. Bull.* **1983**, *31*, 2321−2328. (d) Supriyono, A.; Schwarz, B.; Wray, V.; Witte, L.; Muller, W. E. G., van Soest, R.; Sumaryono, W.; Proksch, P. *Z. Naturforsch*. **1995**, *50c*, 669−674. (e) Williams, D. H.; Faulkner, D. J. *Nat. Prod. Lett.* **1996**, *9*, 57−64. (f) Eder, C.; Proksch, P.; Wray, V.; Steube, K.; Bringmann, G.; van Soest, R. W. M.; Sudarsono; Ferdinandus, E.; Pattisina, L. A.; Wiryowidagdo, S.; Moka, W. *J. Nat. Prod.* **1999**, *62*, 184−187.

(5) (a) Xu, Y.-z.; Yakushijin, K.; Horne, D. A. *J. Org. Chem*. **1997**, *62*, 456−464. (b) Barrios Sosa, A. C.; Yakushijin, K.; Horne, D. A. *J. Org. Chem*. **2000**, *65*, 610−611.

(6) Kobayashi, J.; Ohizumi Y.; Nakamura H.; Hirata, Y.; Wakamatsu, K.; Miyazawa, T. *Experientia* **1986**, *42*, 1064−1065.

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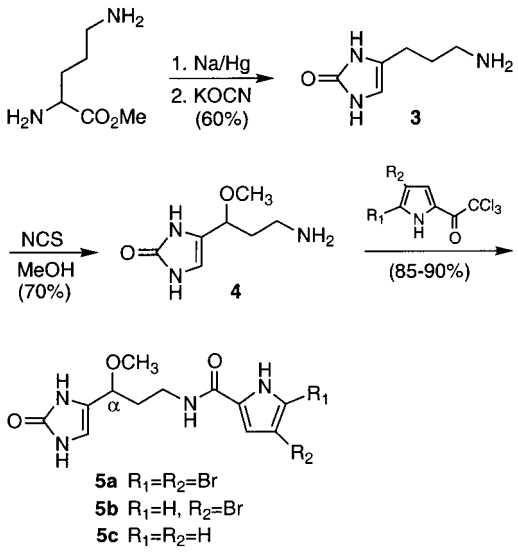
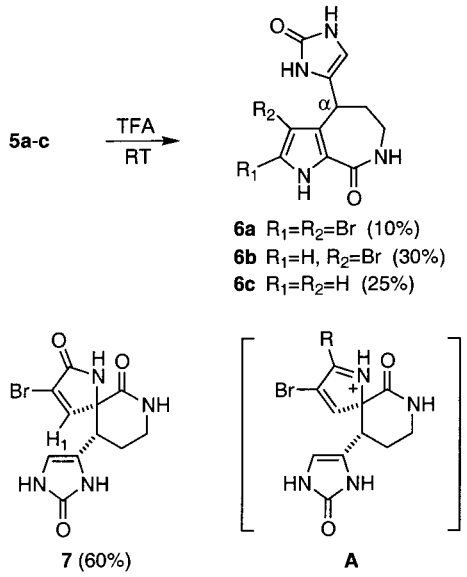
Scheme 1



Scheme 2



intramolecular cyclization event would establish the formation of the pyrroloazepinone core (Scheme 1). Initial investigations focused on the preparation of **5**. Starting from commercially available ornithine as its methyl ester, aminopropyl imidazolone **3** was obtained in good yield after a two-step, single-pot sequence that involves an Akabori reduction followed by condensation with potassium cyanate.[7] Introduction of the α-methoxy substituent was achieved by treatment of **3** with NCS in methanol. This produced oxidized imidazolone **4** in good yield.[8] Acylation of **4** with the requisite trichloroacetyl pyrrole[9] gave carboxamides **5a**−**c**.

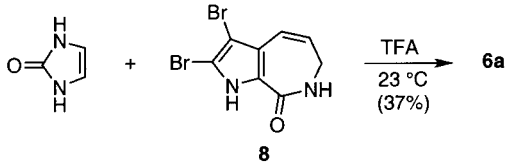
Next, the acid-facilitated intramolecular cyclization of **5** to **6** was investigated (Scheme 2). This key step forms the basis of our approach to the tricyclic pyrroloazepinone framework that comprises axinohydantoins. Exposure of

(7) Originally performed with thiocyanate, see: (a) Akabori, S. *Ber.* **1933**, *66*, 151−165. (b) Lawson, A.; Morley, H. V. *J. Chem. Soc.* **1955**, 1695−1698.

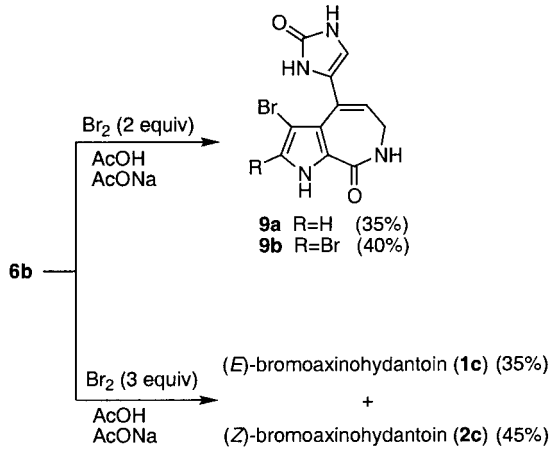
(8) Barrios Sosa., A. C.; Yakushijin, K., Horne, D. A. *Org. Lett.* **2000**, *2*, 3443−3444.

(9) Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300−1302.

Scheme 3



Scheme 4

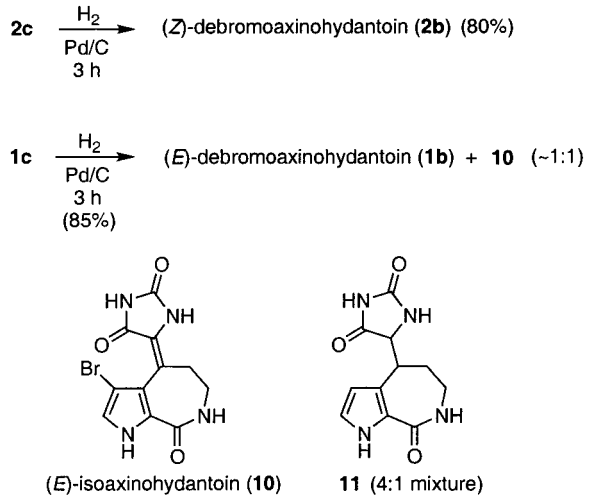


dibromopyrrole carboxamide **5a** to trifluoroacetic acid produced only a minor amount (10%) of the desired product **6a**. The major product of the reaction is spirolactam **7** which was isolated in 60% yield. The relative stereochemistry of **7** was determined from NOE data which suggested a cis orientation of H_1 and the imidazolone ring. Hydrolysis of the bromoimine functionality of proposed intermediate **A** (R = Br) is thought to account for the formation of spirolactam **7**. In an attempt to increase the yield of desired tricyclic azepinone framework of **6**, cyclization of α-debromopyrrole analogues **5b** and **5c** was pursued. These analogues lack an α-bromopyrrole substituent and should not undergo hydrolysis to the spirolactam. Thus, intermediate **A** (R = H) could undergo potential rearrangement to the pyrroloazepinone skeleton either by a 1,2-alkyl shift or through a reversible ring opening−cyclization process. When α-debromo analogues **5b** and **5c** were subjected to the cyclization conditions, a modest 2−3-fold increase in yield of azepinones **6b** and **6c** was observed.

In an alternative approach for assembling the tricyclic core of **6a**, the heterodimerization of commercially available 2-imidazolone and bicyclic olefin **8** was pursued (Scheme 3). This approach is patterned after a similar reaction of **8** with 2-aminoimidazole, which resulted in an efficient synthesis of hyemin.[5] In the present case, however, the use of 2-imidazolone was only partially successful. 2-Imidazolone, unlike 2-aminoimidazole, is prone to self-dimerization under acidic conditions, and this process is accelerated in strong acids such as CH_3SO_3H. Using trifluoroacetic acid, however, a 37% yield of azepinone **6a** was obtained from the reaction of **8** and 2-imidazolone. Although the yield is modest, unreacted starting material **8** can be recovered and recycled for further use.

With tricyclic azepinones **6** in hand, the conversion of the imidazolone unit to the requisite hydantoin was pursued (Scheme 4). Using related conditions developed for the installation of the α,β-unsaturated imidazolidinone (glycocyamidine) functionality in hymenialdisines,[5b]

Scheme 5



treatment of imidazolone **6b** with 2 equiv of bromine in a sodium acetate/acetic acid medium produced a mixture of mono- and dibrominated unsaturated pyrroloazepinones **9a** and **9b** in 35% and 40% yields, respectively. Small amounts (<10%) of the desired (*E*)- and (*Z*)-bromoaxinohydantoins **1c** and **2c** could be detected. These results suggest that pyrrole bromination effectively competes with bromination of the imidazolone unit. Increasing the amount of bromine to 3 equiv produced the desired products, (*E*)- and (*Z*)-bromoaxinohydantoins **1c** and **2c** in 35% and 45% yields, respectively, after flash chromatography. Similar treatment of dibromoazepinone **6a** with 2 equiv of bromine afforded (*E*)- and (*Z*)-isomers **1c** and **2c**. The (*E*)- and (*Z*)-geometry of the tetrasubstituted double bond at C-10 was deduced from comparison of the reported carbon[3b] and proton[4e] chemical shift of C-9. Interestingly, in contrast to the oxidation of hymenin to bromohymenialdisine[5b] which produced only the (*Z*)-glycocyamidine isomer, both (*E*)- and (*Z*)-hydantoin isomers were obtained from oxidation of imidazolones **6a** and **6b**. These results suggest that hydantoin-containing (*E*)-axinohydantoins are configurationally more stable than their glycocyamidine-containing (*E*)-hymenialdisine counterparts.

Next, chemoselective hydrogenation of **1c** and **2c** was investigated (Scheme 5). While reduction of (*Z*)-bromoaxinohydantoin (**2c**) produced (*Z*)-debromoaxinohydantoin (**2b**) in good yield, the reduction of (*E*)-isomer **1c** afforded, surprisingly, a 1:1.3 mixture of (*E*)-debromoaxinohydantoin (**1b**) and the mono-reduction product, (*E*)-isoaxinohydantoin (**10**). Spectroscopic data of synthetic **2b** was in agreement with data reported for the natural material.[3] Attempts to drive the debromination to completion using longer reaction times (8 h) led to competing reduction of the C10−C11 double bond which produced **11** as a 4:1 mixture of diastereomers. An explanation for the observed difference in reactivity of isomers **1c** and **2c** remains elusive at this time. One possibility is steric interactions between the (*E*)-hydantoin appendage and the catalyst may hinder complete removal of the 3-bromine substituent prior to over-reduction.

Finally, (*E*)-bromoaxinohydantoin (**1c**) was found to undergo slow isomerization to the corresponding *Z*-isomer **2c** in DMSO-d_6 at room temperature (T = 6 d, ~30% isomerization). Heats of formation derived from AM1 semiempirical calculations revealed that the *Z*-isomer **1c** is approximately 6 kcal/mol lower in energy than the corresponding *E*-isomer **2c**. Similar findings were observed between the (*E*)- and (*Z*)-isomers of monobrominated and debrominated analogues **10** and **1b**. These data suggest that presence of bromine atoms on the pyrrole (steric factors) is not a predominant factor in determining the energy differences between the (*E*)- and (*Z*)-isomers.

In summary, a short synthesis of (*E*)- and (*Z*)-axinohydantoins **1b**, **1c**, **2b**, and **2c** has been achieved. The established route provides access to a number of previously unprecedented axinohydantoin derivatives. The α-functionalized cyclization of linear precursor **5** to the tricyclic azepinone framework of **6** may, in fact, model a biosynthetic cyclization step common to these natural products and related pyrroloazepinone metabolites (e.g., hymenin). Furthermore, we have shown that the 2-imidazolone nucleus, which is readily available from α-amino acids, serves as a useful precursor to the hydantoin structural unit.

Acknowledgment. Financial Support from the National Institutes of Health and Chugai Pharmaceutical Co. is gratefully acknowledged.

Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR spectra for compounds **1b**, **1c**, **2b**, **2c**, **3**, **4**, **5a**−**c**, **6a**−**c**, **7**, **9a**, **9b**, **10**, and **11** are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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