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Synthesis of dibromophakellstatin and dibromoisophakellin

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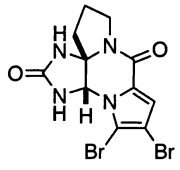
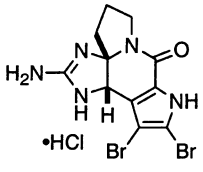
Abstract—A short synthesis of the marine sponge alkaloids dibromophakellstatin (**1**) and dibromoisophakellin (**2**) is described. The synthesis of **1** centers on a putative biomimetic oxidative cyclization of imidazolone **5**. Thermal rearrangement of dibromophakellin (**9**) in the presence of K_2CO_3 afforded dibromoisophakellin (**2**).

Marine sponges continue to be a source of structurally interesting and biologically active nitrogen heterocyclic metabolites.[1] Recently, Pettit and co-workers isolated dibromophakellstatin (**1**) from the sponge, *Phakellia mauritiana*.[2] **1** has been shown to posses potent antitumor activity in a number of different human cell-lines. The structurally related sponge metabolite dibromoisophakellin (**2**) was isolated from *Acanthella carteri* by Maximov and co-workers.[3] Structures of **1** and **2** were elucidated by X-ray crystallographic analysis. Neither metabolite has been synthesized; however, a synthetic approach to **1** has appeared recently in the literature.[4] In this communication, we report the first synthesis of racemic **1** and **2** using a biomimetic oxidative cyclization protocol that sets the stage for construction of the tetracyclic framework.



dibromophakellstatin (**1**)



dibromoisophakellin (**2**)

Although the biosynthesis of dibromophakellstatin (**1**) is unknown, aminopropyl imidazolone **4** was envisioned as a hypothetical forerunner. We have shown that **4** is a useful intermediate in the putative biomimetic syntheses of related imidazolone derived sponge metabolites, slagenins[5] and axinohydantoins.[6] **4** is readily prepared from ornithine methyl ester (**3**) via Akabori reduction and condensation with cyanate (Scheme 1). Acylation of the free base of **4** with 2,3-dibromo(trichloroacetyl)pyrrole[7] gave carboxamide **5** in excellent yield. After considerable experimentation, oxidation of **5** with NBS (trifluoroacetic acid, 0°C, 5 min) followed by concentration and addition of triethylamine:THF (1:1) produced dibromophakellstatin (**1**) and spiro adduct **6**[8] in 45 and 40% yields, respectively. These products are easily separated by flash chromatography. All spectral data of synthetic **1** were in agreement with those reported for the natural product.[2] Hydrogenolysis of **1** produced phakellstatin (**7**).[9]

Next, attempts were made to synthesize dibromoisophakellin (**2**) from dihydrooroidin (**8**)[10] (Scheme 2). An interesting structural feature of **2** is the fused C–C pyrrole connection to the cyclic guanidine core. There are several notable natural products such as styloguanidines[11] and 12-chloro-11-hydroxydibromoisophakellin[12] that contain an isophakellin structural motif for which no prior synthesis has been reported.[13] In the elegant biomimetic synthesis of dibromophakellin (**9**) by Büchi,[14] bromine oxidation of **8** followed by treatment with KO^{t}Bu did not lead to any C–C pyrrole products resembling dibromoisophakellin (**2**). In further pursuing this line of research, we were also unable to produce **2** directly from **8** under various experimental conditions. It was discovered, however, that the use of NBS in TFA followed by evaporation and quenching with TEA:THF (1:1) gave excellent yields of racemic dibromophakellin (**9**).[15] These conditions represent a noteworthy improvement over the original Büchi conditions of Br_2/AcOH. Using a less reactive brominating reagent such as NBS and a stronger acid (TFA), substantially higher yields of product were obtained for both the imidazolone and aminoimidazole series. In fact, we were unable to obtained dibromophakellstatin (**1**) from **5** using Br_2/AcOH. Quenching the intermediate derived from oxidized **8** with MeOH produced spiro adduct **10**.[16]

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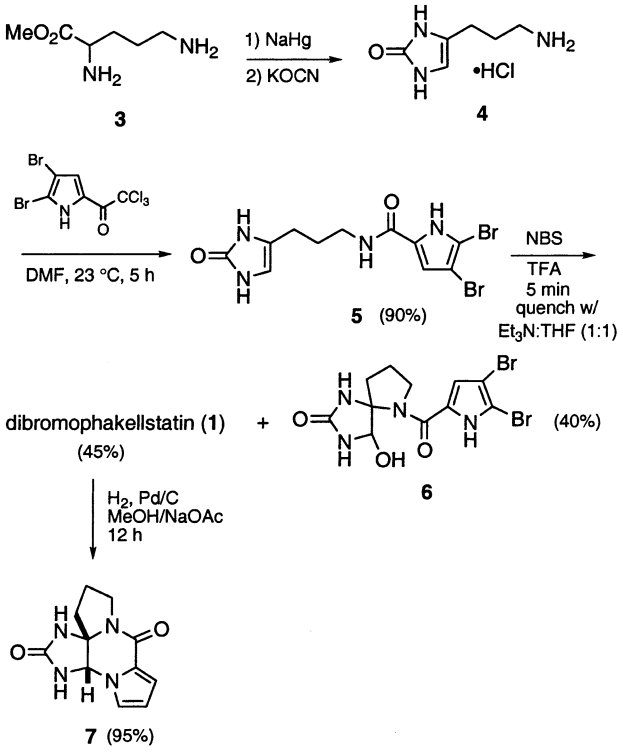
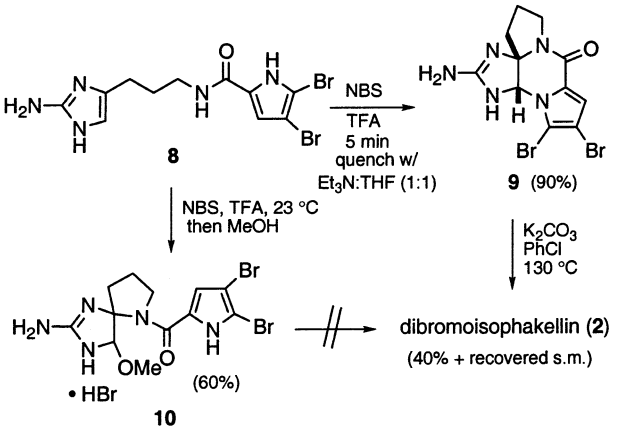


Scheme 1.



Scheme 2.

Attempts to convert **10** to dibromoisophakellin (**2**) were unsuccessful.

Finally, heating dibromophakellin (**9**) in the presence of K_2CO_3 caused N to C rearrangement to dibromoisophakellin (**2**) plus recovered starting material. All spectral data of synthetic **2** were in agreement with those reported for the natural product.[3,17] While the rearrangement of dibromophakellin represents the first successful segway to the isophakellin series, clearly, more efficient methods will be needed for the more structurally challenging styloguanidine family.

Acknowledgements

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References

1. Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1–49 and references cited therein.
2. Pettit, G. R.; McNulty, J.; Herald, D. L.; Doubek, D. L.; Chapuis, J. C.; Schmidt, J. M.; Tackett, L. P.; Boyd, M. R. *J. Nat. Prod.* **1997**, *60*, 180–183.
3. Fedoreyev, S. A.; Utkina, N. K.; Ilyin, S. G.; Reshetnyak, M. V.; Maximov, O. B. *Tetrahedron Lett.* **1986**, *27*, 3177–3180.
4. Jacquot, D. E. N.; Hoffman, H.; Polburn, K.; Lindel, T. *Tetrahedron Lett.* **2002**, *43*, 3699–3702.
5. Barrios Sosa, A. C.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 3443–3444.
6. Barrios Sosa, A. C.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.*, in press.
7. Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300–1302.
8. Compound **6**: ^{1}H NMR (acetone-d_6) 11.89* (bs, 1H), 7.65* (bs, 1H), 6.74 (d, $J=2.2$ Hz, 1H), 6.54* (bs, 1H), 5.52 (m, 1H), 5.46* (d, $J=5.3$ Hz, 1H), 3.87–3.75 (m, 1H), 3.65–3.58 (m, 1H), 2.68–2.59 (m, 1H), 2.04–1.93 (m, 1H), 1.88–1.76 (m, 2H). *D_2O exchangeable. ^{13}C NMR (acetone-d_6) 161.9 (s), 159.0 (s), 128.4 (s), 115.6 (d), 106.3 (s), 99.2 (s), 85.4 (s), 82.5 (d), 49.2 (t), 33.6 (t), 23.3 (t).
9. Compound **7**: ^{1}H NMR (DMSO-d_6) 8.13* (bs, 1H), 7.79* (bs, 1H), 7.11 (m, 1H), 6.65 (m, 1H), 6.26 (m, 1H), 5.74 (s, 1H), 3.55–3.38 (m, 2H), 2.25–1.94 (m, 4H). *D_2O exchangeable. ^{13}C NMR (DMSO-d_6) 159.6 (s), 156.5 (s), 124.1 (s), 122.7 (d), 112.1 (d), 111.6 (d), 79.5 (s), 68.5 (d), 45.2 (t), 39.5 (t), 20.3 (t).
10. Olofson, A.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.* **1998**, *63*, 1248–1253.
11. Kato, T.; Shizuri, Y.; Izumida, H.; Yokoyama, A.; Endo, M. *Tetrahedron Lett.* **1995**, *36*, 2133–2136.
12. Tsukamoto, S.; Kazuhiro, T.; Ohta, T.; Matsunga, S.; Fusetani, N.; van Soest, R. W. M. *J. Nat. Prod.* **2001**, *64*, 1576–1578.
13. For a synthetic approach to the bisguanidine alkaloids styloguanidine and palau'amine, see: (a) Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159–7160; (b) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535–1538.
14. Foley, L. H.; Büchi, G. *J. Am. Chem. Soc.* **1982**, *104*, 1776–1777.
15. (a) Sharma, G. M.; Burkholder, P. R. *Chem. Commun.* **1971**, *1*, 151–152; (b) Sharma, G.; Magdoff-Fairchild, B. *J. Org. Chem.* **1977**, *42*, 4118–4124.
16. Compound **10**: ^{1}H NMR (DMSO-d_6) 12.75* (bs, 1H), 10.08* (bs, 1H), 9.56* (bs, 1H), 8.33* (bs, 2H), 6.83 (s, 1H), 5.07 (s, 1H), 3.78–3.74 (m, 2H), 3.32 (s, 3H), 2.46–2.37 (m, 1H), 1.98–1.79 (m, 3H). *D_2O exchangeable. ^{13}C NMR (DMSO-d_6) 159.7 (s), 159.3 (s), 128.5 (s), 116.3 (d), 107.4 (s), 99.1 (s), 91.8 (d), 86.3 (s), 56.9 (q), 49.8 (t), 33.5 (t), 23.7 (t).
17. The following revised ^{13}C NMR assignments for dibromoisophakellin (**2**) are more consistent with the structure than those reported in Ref. 3: δ 96.5 (s, C-3), 108. 6 (s, C-2), 122.6 and 122.8 (s×2, C-4 and C-5).