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Transbromination of Brominated Pyrrole and Imidazole Derivatives: Synthesis of the $C_{11}N_5$ Marine Alkaloid Stevensine

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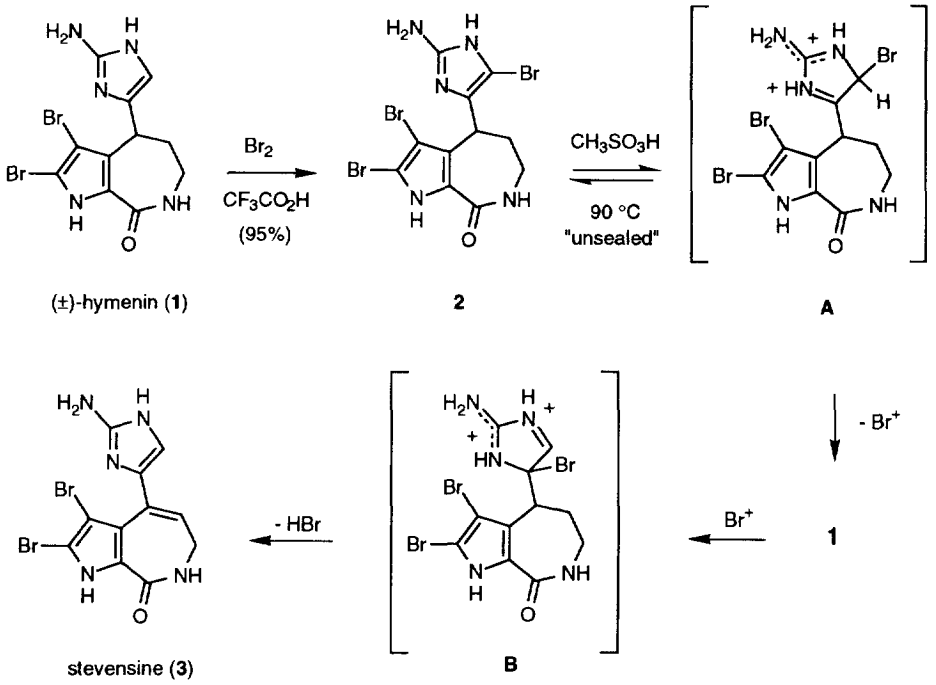
Abstract: The marine sponge alkaloid stevensine (**3**) has been synthesized from the related $C_{11}N_5$ alkaloid, hymenin (**1**). The key transformation involves a regioselective protodebromination/transbromination event of 4'-bromohymenin (**2**) to install the olefin in **3**. Such processes are seldom used for synthetic purposes but appear to be highly applicable to the $C_{11}N_5$ family of marine alkaloids. Copyright © 1996 Elsevier Science Ltd

A well-known process often associated with Friedel-Crafts catalysis involving aryl bromides is protodebromination and bromine migration.[1] Although the process is seldom adapted for synthetic purposes, it may prove important in relation to certain bromine substituted marine alkaloids that are based on pyrrole, indole, and β-carboline units.[2] The difficulty in preparation of these derivatives by conventional electrophilic aromatic substitution reactions attests to its potential significance. Curiously, there have been no reports on the isolation of brominated 2-aminoimidazole metabolites, but rather, it is their hydrolyzed derivatives, 2-aminoimidazolones, that are quite common among marine natural products.[2] In this communication, we describe the use of a brominated 2-aminoimidazole derivative, namely 4'-bromohymenin (**2**), in the synthesis of the $C_{11}N_5$ sponge metabolite, stevensine (**3**).[3,4] A thermally assisted protodebromination and bromine migration process (termed transbromination) involving **2** was used to install the olefin contained in **3**.

In accordance with the relative basicities of the two classes of heterocycles, pyrroles and 2-aminoimidazoles, it was anticipated that brominated 2-aminoimidazoles would possess a higher degree of reactivity in processes involving ring protonation to afford sigma complexes. The following is illustrative. 4'-Bromohymenin (**2**) can be prepared in quantitative yield by direct bromination of hymenin (**1**)[5,6] in trifluoroacetic acid (Scheme 1).[7] Upon heating in methanesulfonic acid (90 °C, 24 h) in an *unsealed* flask, **2** produced both hymenin (**1**) (40%) and stevensine (**3**) (20%). Spectral data of synthetic **3** were in complete agreement with those reported for the natural product.[3] The production of **1** and **3** may follow a disproportionation-like mechanism.[8] The reduction product, **1**, results from protodebromination of the 2-aminoimidazole (AI) ring presumably via intermediate **A**. Oxidation of **1** by Br^+ generated *in situ* leads to the postulated ipso intermediate, **B**. Elimination of HBr and aromatization affords stevensine (**3**). All attempts to effect the direct oxidation of **1** to **3** were unsuccessful and resulted in the formation of overoxidized products.

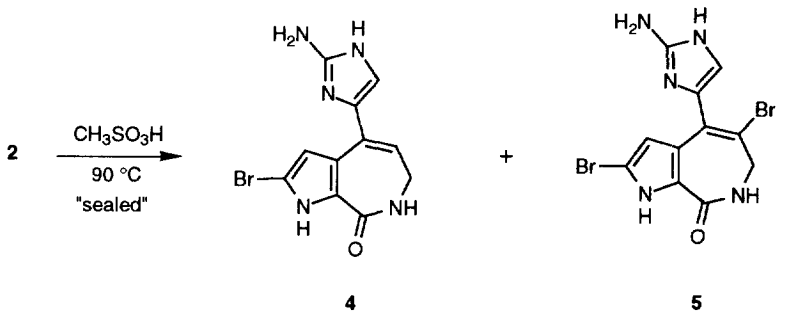
Interestingly, when the analogous protodebromination reaction of **2** was carried out under *sealed* conditions, debromination of both the aminoimidazole and pyrrole units occured. 3-Debromostevensine (**4**) and 5-bromo-3-debromostevensine (**5**) were obtained in 7% and 58% yields, respectively (Scheme 2). Under sealed conditions, the HBr formed in the reaction is now contained within the reaction mixture and functioned as a reducing agent to cause additional hydrodebromination of the pyrrole units in the initial products **1** and **3**. This led to isolated products **4** and **5**.

Scheme 1



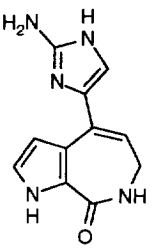
The position of hydrodebromination on the pyrrole ring was determined from the ^1H NMR spectra of the HCl salts of **4** and **5** which have β hydrogen signals at 6.40 (s) and 6.13 (s) ppm in CD_3OD, respectively. This can be compared with α-pyrrole hydrogen signals of related bromo derivatives which are typically observed at lower fields around, 6.9 ppm. The slight downfield shift for the β hydrogen of **4** compared to **5** is probably a reflection of a more planar arrangement of the AI ring in **4** with respect to the bicyclic core.

Scheme 2



It is interesting to note that while the pyrrole bromines were unreactive towards methanesulfonic acid, the bromine atom substituted on the 2-aminoimidazole ring underwent facile protodebromination.

These results suggested that while the pyrrole unit in hymenin (**1**) is stable in the presence of methanesulfonic acid, it should undergo a protodebromination/transbromination process in the presence of HBr. Indeed this was the case. When a solution of hymenin (**1**) in methanesulfonic acid was treated with a catalytic amount of HBr and heated in a sealed flask, a series of disproportionation-like products were isolated. These products included 3-debromostevensine (**4**) (10%), 5-bromo-3-debromostevensine (**5**) (45%), 2,3-debromostevensine (**6**) (8%), and 5-bromostevensine (**7**) (5%). Comparison of the α and β positions of these 2-acyl-substituted pyrrole rings, the β position was consistently the more reactive site towards protodebromination. This resulted in the selective removal of Br in the β position while leaving the α position intact. Both positions, however, can be debrominated under forcing conditions.



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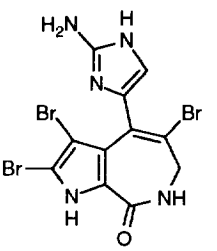

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In conclusion, two interesting findings resulted from this investigation. First, protodebromination of dibrominated pyrroles occurs preferentially to afford α-bromo substituted pyrrole derivatives. The preparation of such substitution is difficult by conventional methods involving the direct a bromination of a debromo precursor.[9] The more favorable β bromination for these 2-acyl debromopyrrole derivatives undoubtedly accounts for the formation of the majority of monobromo $C_{11}N_5$ and related series of marine alkaloids isolated to date.[2] Extension of the protodebromination strategy may be useful for the preparation of α-bromo substituted derivatives such as the one seen in the anti-tumor $C_{11}N_5$ marine alkaloid hymenialdisine.[10] Second, in the case of brominated aminoimidazole, the proposed ipso intermediate in the Br migration process resulted in side-chain oxidation products as observed in the formation of olefins **3-7**. Application of this finding to related guanidine based marine alkaloids are forthcoming. And finally, the seldom used protodebromination and bromine migration strategy may find useful applications in other heterocyclic systems such as those based on indole.

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7. All new compounds gave satisfactory spectral and analytical data. ^{1}H and ^{13}C NMR data were collected at 400 and 75.1 MHz, respectively, and are listed below for compounds **2**, **4-7**.

   4'-Bromohymenin (**2**)•HCl: ^{1}H NMR (CD_3OD) δ 2.21-2.13 (m, 2H), 2.33-2.24 (m, 2H), 3.35-3.25 (m 2H), 4.25 (dd, 1H, J = 6.8, 5.5); ^{13}C NMR (CD_3OD) δ 34.3 (t), 36.5 (d), 39.6 (t), 96.2 (s), 102.4 (s), 108.6 (s), 124.7 (s), 126.1 (s), 127.4 (s), 148.9 (s), 164.0 (s).

   3-Debromostevensine (**4**)•HCl: ^{1}H NMR (CD_3OD) δ 3.61 (d, 2H, J = 7.0), 6.14 (t, 1H, J = 7.0), 6.40 (s, 1H), 6.86 (s, 1H); ^{13}C NMR (CD_3OD) δ 39.3, 107.1, 111.7, 112.8, 122.5, 126.1, 127.7, 128.1, 128.7, 149.1, 164.9.

   5-Bromo-3-debromostevensine (**5**)•HCl: ^{1}H NMR (CD_3OD) δ 4.14 (s, 2H), 6.13 (s, 1H), 6.97 (s, 1H); ^{13}C NMR (CD_3OD) δ 50.7 (e), 107.2 (e), 112.2 (o), 115.3 (o), 118.4 (e), 125.6 (e), 127.3 (e), 127.6 (e), 127.7 (e), 148.6 (e), 164.3 (e).

   2,3-Debromostevensine (**6**)•HCl: ^{1}H NMR (CD_3OD) δ 3.61 (d, 2H, J = 7.0), 6.13 (t, 1H, J = 7.0), 6.40 (d 1H, J = 2.8), 6.84 (s, 1H), 7.09 (d, 1H, J = 2.8); ^{13}C NMR (CD_3OD) δ 39.3, 109.6, 112.7, 121.5, 123.7, 124.3, 127.0, 128.4, 129.6, 149.1, 166.1.

   5-Bromostevensine (**7**): ^{1}H NMR (CD_3OD) δ 4.12 (s, 2H), 6.92 (s, 1H); ^{13}C NMR (CD_3OD) δ 50.4, 99.9, 110.0, 116.0, 121.1, 124.3, 124.5, 125.8, 128.8, 148.6, 163.6.
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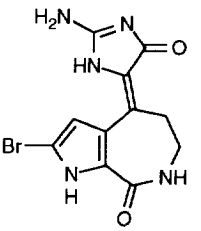

hymenialdisine

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