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Synthesis of Dispacamide from the Marine Sponge *Agelas dispar*

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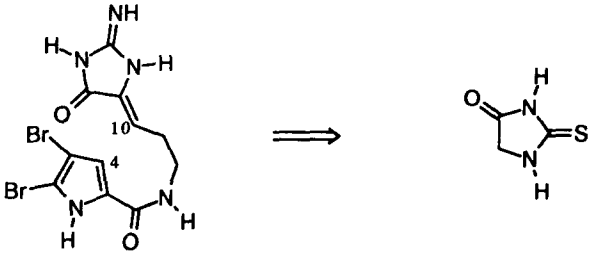
Abstract: The marine natural product dispacamide (**1**) has been synthesized for the first time starting from 2-thiohydantoin (**2**). A facile one pot conversion of alkylidene thiohydantoins to the corresponding 2-iminoimidazolones is described employing *tert.*-butylhydroperoxide (TBHP) in the presence of aqueous ammonia.

The exploration of marine natural products continues to make promising contributions to life sciences.[1] Dispacamide (**1**) from the sponge *Agelas dispar*[2] belongs to a family of biogenetically related, exclusively marine alkaloids sharing a pyrrole ring connected to an imidazole moiety through a five-membered chain. **1** is assumed to be the direct precursor of marine pyrroloazepinones such as the hymenialdisines[3] through bond formation between C-4 and C-10. A short-step synthesis of the anti-histaminic dispacamide (**1**) is essential for advanced studies towards the chemistry and the biological activities of the oroidin alkaloids.[4]

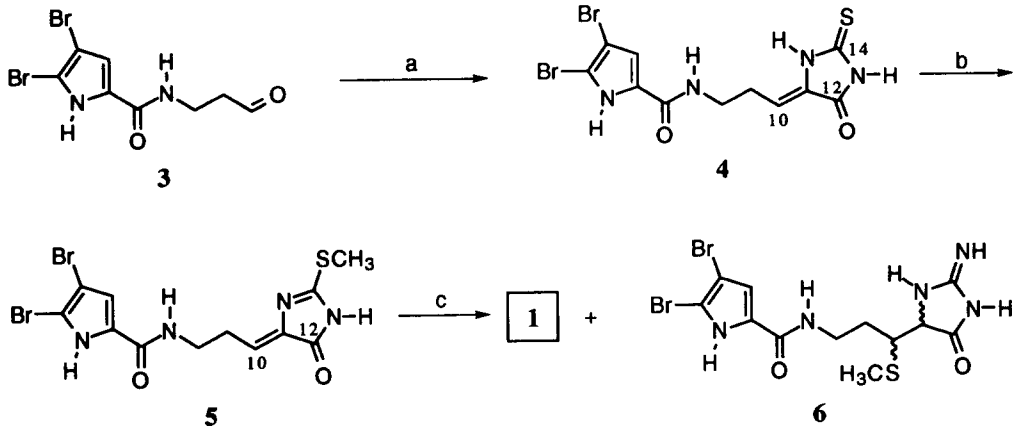


1: Dispacamide **2**

Scheme 1. 2-Thiohydantoin (**2**) as synthetic precursor of the marine natural product dispacamide (**1**).

Attempts to directly couple 2-amino-4-imidazolone (glycocyamidine) with the aliphatic aldehyde **3**[5] failed.[6] However, condensation of **3** with 2-thiohydantoin (**2**) in the presence of piperidine[7] conveniently provided stereochemically pure[8] (*Z*)-alkylidene thiohydantoin **4** after acidic work-up. Regioselective S-methylation yielded the mercapto imidazolone **5** with retention of the stereochemistry. On treatment of **5** with NH_3/NH_4Cl in

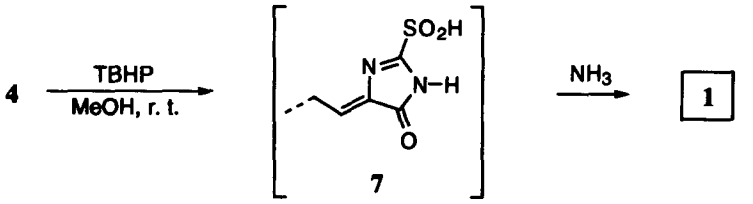
methanol under elevated pressure and temperature,[9] a product mixture was obtained with dispacamide (**1**) being the major constituent. NMR and MS analysis revealed that both diastereomers of the mercaptane **6** were formed as side products in substantial amounts (**1** : **6** ≈ 60 : 40). In the ^{1}H NMR spectrum of the mixture of **1** and **6**, two pairs of methine protons appeared at δ 3.00, 4.33 *resp.* δ 3.00, 4.24. Under the reaction conditions, methylmercaptane formed in the primary ammonolysis had to remain in solution and obviously was available for a subsequent Michael addition to dispacamide (**1**). Tedious separation through preparative reversed phase HPLC (RP-18, phosphate buffer pH 7.8/MeOH) allowed to obtain pure material of **1**.



Scheme 2. Synthesis and ammonolysis of the mercapto imidazolone **5**. a: **2**, piperidine, EtOH/H_2O (8:2), r. t., 4 h, 80 %; b: CH_3I, K_2CO_3, dry DMF, 0° C, 2 h, 75 %; c: NH_3 (sat.)/NH_4Cl (2 equiv.), dry MeOH, sealed tube, 60° C, 7 h, 80 % (**1**:**6** ≈ 60:40).

Electrophilic activation of C-14 through oxidation of the sulfur substituent proved to be the key to the chemoselective synthesis of dispacamide (**1**). We discovered that the use of *tert.*-butylhydroperoxide (TBHP) and aqueous ammonia in methanol at room temperature gives efficient access to **1** without significant formation of side products. Mass spectral analysis (HRFABMS) confirmed the sum formula of dispacamide (**1**). The (*E*)-isomer of dispacamide (**1**) appears to be formed initially[10] and to then undergo isomerization to the natural product on irradiation.[11] The ^{1}H and ^{13}C NMR data of the isomerized product were identical with those reported for dispacamide (**1**).[2] The aminoiminomethanesulfinic acid **7** *resp.* its tautomers can be proposed as probable reaction intermediates,[12] because it was found that exactly two equivalents of TBHP are required to achieve complete conversion. The use of three equivalents of TBHP accelerates the reaction. Model transaminations were successfully carried out on 5-alkylidene-2-thiohydantoins derived from acetone, benzaldehyde, and acetic

aldehyde, while the transformation failed for 2-thiohydantoin (**2**) itself.



Scheme 3. One pot transamination of the alkylidene thiohydantoin **4**.

Experimental procedure: The alkylidene thiohydantoin **4** (1.26 g, 3.00 mmol) was suspended in methanol (120 ml) and aqueous ammonia (25 %, 4.30 g, 250 mmol, 15.0 ml) was added at room temperature, followed by aqueous TBHP (70 %, 1.16 g, 1.23 ml, 9.00 mmol). After stirring at room temperature for 12 h, the starting material was completely dissolved and the solution was filtered. The solvents were removed under reduced pressure and the residue was purified by column chromatography ($CHCl_3$/MeOH/aq. NH_3 40:20:1). The pure fraction was dissolved in acetone/water (3:1) and the acetone was evaporated at room temperature to obtain **1** as a colorless precipitate. Yield: 874 mg (72 %).

In summary, the marine natural product dispacamide (**1**) was synthesized within two steps in an overall yield of about 50 % *via* direct transamination of the 5-alkylidene-2-thiohydantoin **4** employing aq. NH_3 in the presence of 2 equiv. of TBHP. Besides the high efficiency of this newly introduced one pot procedure, the alternate reaction sequence towards dispacamide (**1**) is shortened by one step, because the S-methylation of **4** becomes obsolete. The Michael addition of methylmercaptane to dispacamide (**1**) supports its possible role as biosynthetic and as synthetic precursor of the oroidin alkaloid hymenialdisine.[3]

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10. (*E*)-Dispacamide: ^{1}H NMR ([D$_4$]methanol, 360 MHz): δ = 2.53 (dt, J = 7.1, 7.1 Hz, 2 H, 9-H$_2$), 3.47 (t, J = 7.1 Hz, 2 H, 8-H$_2$), 5.82 (t, J = 7.1 Hz, 1 H, 10-H), 6.82 (s, 1 H, 4-H). - ^{13}C NMR ([D$_4$]methanol, 90.6 MHz): δ = 28.7 (C-9), 39.4 (C-8), 100.1 (C-3), 106.2 (C-2), 113.6 (C-10), 114.5 (C-4), 128.7 (C-5), 135.2 (C-11), 161.9 (C-6), 165.3 (C-14), 175.2 (C-12). - MS (FAB, positive ions, NBA); *m/z* (%): 404/406/408 (4/9/5) [M$^+$ + H]. - HRFABMS $C_{11}H_{12}{}^{79}Br^{81}BrN_5O_2$ calcd. 405.9358, found 405.9370.
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