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An expeditious multigram preparation of the marine protein kinase inhibitor debromohymenialdisine

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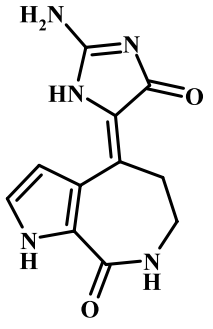
Abstract—A short synthesis of the protein kinase inhibitor debromohymenialdisine is described, which allowed the preparation of several grams of the desired compound.

The interest in marine alkaloids of the pyrroloazepine family was recently renewed with the discovery of their potential mechanism of action: debromohymenialdisine (DBH) **1** was shown to be an inhibitor of the G2 checkpoint ($IC_{50}=8$ μM), which delays cell cycle progression and allows DNA repair. Furthermore, DBH was found to inhibit the checkpoint kinases Chk1 and Chk2 with IC_{50} values of 3 and 3.5 μM, respectively.[1] In order to obtain enough DBH as a reference inhibitor, we tried to develop a simple synthesis that would give several grams of this compound.



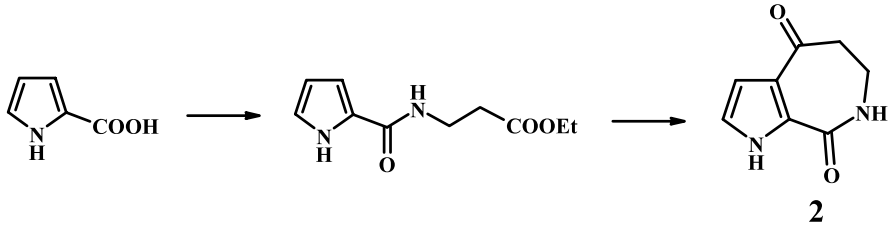
1

The preparation of DBH has already been reported; the first synthesis described by Annoura and Tatsuoka, relies on the preparation of aldisine **2** in three steps starting from 2-pyrrole carboxylic acid (Scheme 1).[2]

After protection of the two nitrogen atoms of **2**, the imidazolone ring was introduced by the preparation of an α-mesyloxy ester, which further reacted with guanidine to give **1**.

In the synthesis published by Horne,[3] the pyrroloazepinone **4** was obtained from dioxolane **3**, itself prepared from pyrrole in 4 steps (Scheme 2).

The aminoimidazole present in hymenine **5** was then converted by oxidative bromination to an imidazoli-



2

Scheme 1.

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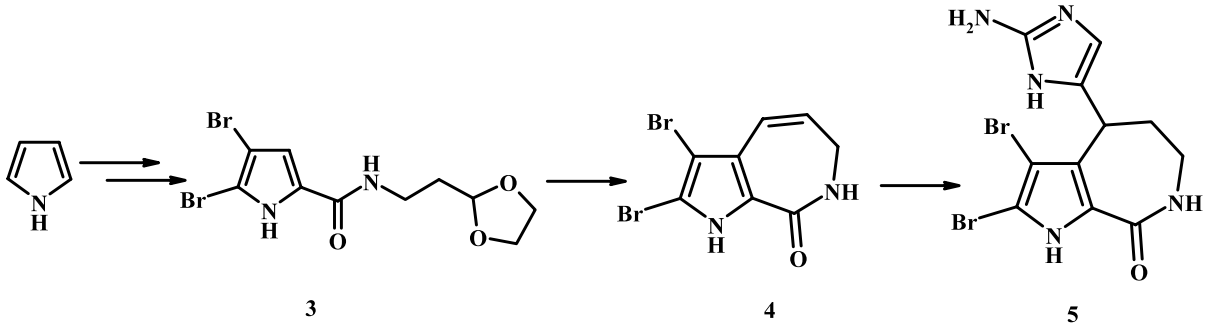
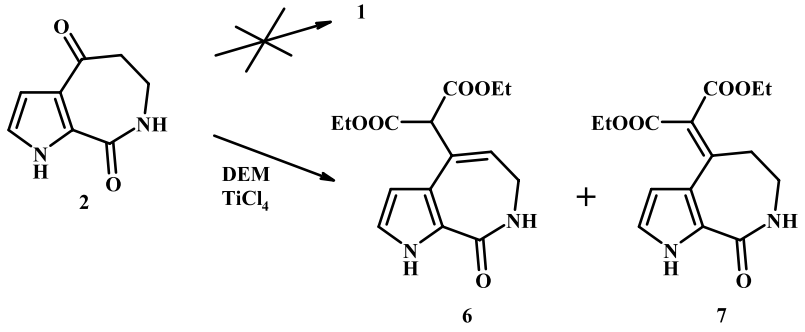


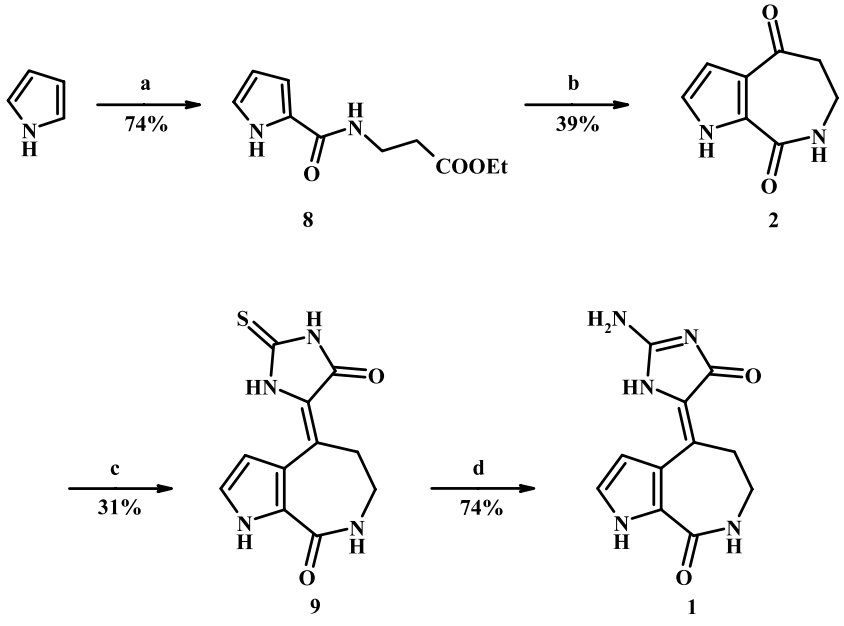
Scheme 2.



Scheme 3.

none ring and DBH was finally obtained after hydrogenolysis of the bromine atoms on the pyrrole ring. Cyclisation of **3** to **4** as well as introduction of 2-aminoimidazole were found to be very time-consuming, lasting 4 and 5 days respectively; moreover, in our hands, the yields were systematically lower than expected, especially the final debromination step during which the exocyclic double bond was significantly reduced. Although this method of obtaining DBH in seven steps from pyrrole appeared attractive, it seemed worthwhile to optimise its preparation.

Interestingly, Prager and Tsopelas described in 1992 their attempts to prepare DBH through the use of aldisine **2**.[4] Condensation of **2** with 2-aminoimidazolinone under different conditions was unsuccessful, but



Scheme 4. *Reagents and conditions*: (a) (i). $Cl_3COCOCl$, dimethylaniline, toluene; (ii). $H_2NCH_2CH_2COOEt$, CH_2Cl_2; (b) (i). NaOH, EtOH; (ii). PPA, P_2O_5; (c) thiohydantoin, $BF_3{\cdot}Et_2O$, Et_3N, THF; (d) NH_4OH, *t*-BuOOH, EtOH.

esters **6** and **7** were prepared by reacting aldisine with diethyl malonate (DEM) in the presence of $TiCl_4$ (Scheme 3).

Starting from pyrrole, we chose to prepare aldisine **2** using the procedure described by Cho (Scheme 4).[5]

Pyrrole was reacted with diphosgene in the presence of dimethylaniline to give the acid chloride. Then a solution of ethyl 3-aminopropionate (or β-alanine ethyl ester) was added in one-pot to give ester **8** in 74% yield for the two steps. Saponification (70%) was followed by cyclisation in polyphosphoric acid (PPA) in the presence of a small amount of P_2O_5 to produce aldisine **2** in 56% yield on a 30 g scale. Aldisine was reacted with thiohydantoin in the presence of $TiCl_4$ and pyridine, but the intermediate **9** was only detected in trace amounts. Replacement of $TiCl_4$ with $BF_3{\cdot}Et_2O$ in the presence of triethylamine[6] gave **9** after chromatography in an unoptimized 31% yield. Finally, DBH was obtained after chromatography in 74% yield by reacting **9** with aqueous ammonia in the presence of *tert*-butylhydroperoxide.[7]

In summary, starting from earlier investigations, we have developed a very simple synthesis that allows the preparation of multigram quantities of DBH. Although several steps deserve further optimisation, the preparation of analogs such as hymenialdisine and dibromohymenialdisine could also be envisioned using this synthetic pathway.

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