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A facile synthesis of (*S*)-gizzerosine, a potent agonist of the histamine H_2-receptor

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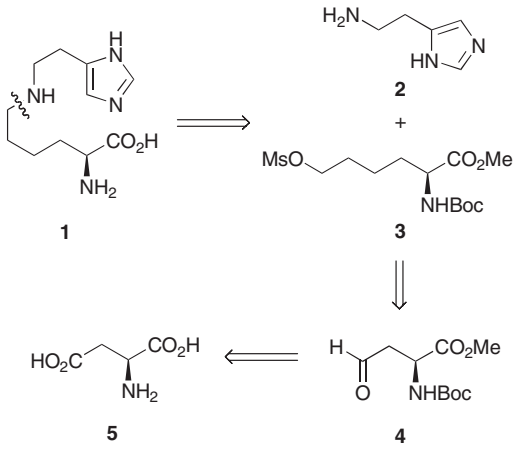
Abstract—A simple and direct approach for the synthesis of (*S*)-gizzerosine, an amino acid responsible for the disease, black vomit, and a potent histamine H_2-receptor, has been developed in 10 steps and in 31% overall yield from L-aspartic acid. The key steps involved a two-carbon homologation of an L-aspartic acid semi-aldehyde and direct alkylation of unprotected histamine with a 6-hydroxynorleucine derivative.

'Black vomit' is a serious disease found worldwide in poultry production and its symptoms include gizzard erosion and ulceration.[1] An investigation into the disease identified brown fishmeal in the diet of affected poultry as the source.[1] Further analysis of the components of heat-treated fishmeal, revealed the α-amino acid, (*S*)-gizzerosine **1** as the toxic agent.[2] As well as being a severe ulcerating agent, biological studies showed that (*S*)-gizzerosine **1** is also a potent agonist for the histamine H_2-receptor and promotes the synthesis of cAMP.[3] These studies suggest that (*S*)-gizzerosine **1** has potential as a drug candidate for the treatment of gastric achlorhydria and osteoporosis.[4]

The significant biological properties of (*S*)-gizzerosine **1** and its relative inaccessibility from fishmeal (0.2 mg per kg) have generated much interest in the development of a practical synthesis of this compound. For example, during their studies in identifying (*S*)-gizzerosine **1** as the cause of the 'black vomit' disease, Mori and co-workers prepared **1** by an enzymatic resolution of α-aminoadipic acid followed by the reductive amination of the subsequent aldehyde with histamine.[2c] More recently, Kiyota and co-workers synthesised **1** using a palladium-catalysed coupling reaction of an amino acid derived allylic acetate with piperonyl-protected histamine.[4,5] We were interested in developing a novel, efficient, scalable approach that introduced the histamine side-chain late in the synthesis and thus, would be flexible enough to allow the generation of analogues for drug discovery. Herein, we now report a ten-step synthesis of (*S*)-gizzerosine from L-aspartic acid that generates a 6-hydroxynorleucine derived mesylate as the key in termediate for efficient coupling with histamine.

Our retrosynthesis of (*S*)-gizzerosine **1** is outlined in Scheme 1. It was proposed that **1** could be prepared by a late stage coupling of unprotected histamine **2** with mesylate **3**. We intended to synthesise **3** from L-aspartic acid **5** by regioselective reduction of the β-carboxylate



Scheme 1.

Keywords: Gizzerosine; Gizzard erosion; Amino acid synthesis; Wittig reaction.
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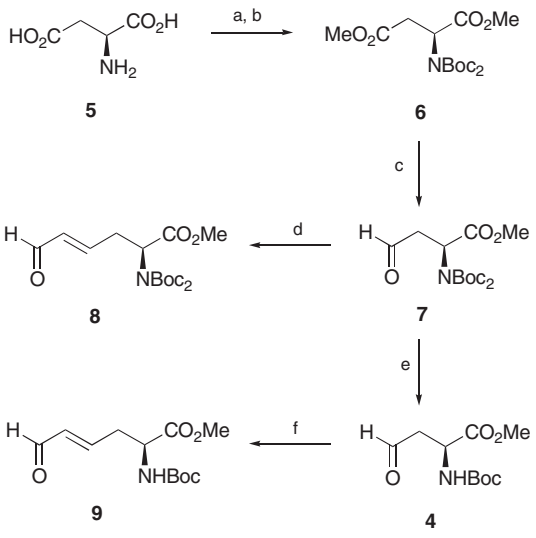
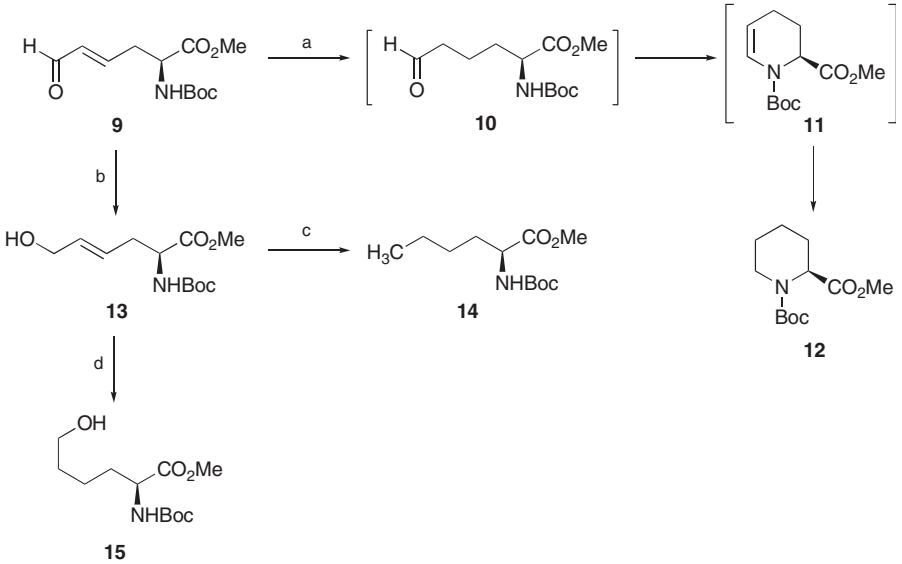
group, followed by a two-carbon homologation and subsequent functional group manipulation.

The first stage of the synthesis involved the preparation of α,β-unsaturated aldehyde **9** (Scheme 2). One-pot esterification and mono-Boc protection of L-aspartic acid was carried out as described by Martín and co-workers.[6] Further treatment with di-*tert*-butyl dicarbonate in the presence of catalytic amounts of DMAP gave *N*,*N*-di-*tert*-butoxycarbonyl L-aspartic acid dimethyl ester **6** in excellent yield. Intermediate **6** has been used a number of times for the synthesis of non-proteinogenic amino acids as the di-Boc protection of the amine allows excellent regioselective manipulation of the ester functional groups.[6a,7] Accordingly, regioselective reduction of the β-methyl ester of **6** using DIBAL-H gave L-aspartic acid semi-aldehyde **7** in 87% yield. The two-carbon homologation of **7** using a Wittig reaction with the stabilised ylide, (triphenylphosphoranylidene)acetaldehyde proved sluggish. Even heating the reaction under reflux for four days gave *E*-α,β-unsaturated aldehyde **8** in only 13% yield. It was proposed that this relatively slow reaction was due to the steric hindrance of the Boc-protecting groups of **7**. Thus, selective removal of one of the Boc-protecting groups was carried out using lithium bromide, which gave the corresponding semi-aldehyde **4** in 89% yield.[8] Subsequent Wittig reaction of **4** with (triphenylphosphoranylidene)acetaldehyde was complete after two days at 35 °C and gave *E*-α,β-unsaturated aldehyde **9** in an excellent 92% yield.



Scheme 2. Reagents and conditions: (a) (i) TMSCl, MeOH; (ii) NEt_3, Boc_2O, 91% over two-steps; (b) Boc_2O, DMAP, MeCN, 100%; (c) DIBAL-H, Et_2O, −78 °C, 87%; (d) $Ph_3P{=}CHCHO$, THF, Δ, 13%; (e) LiBr, MeCN, 89%; (f) $Ph_3P{=}CHCHO$, THF, 35 °C, 92%.

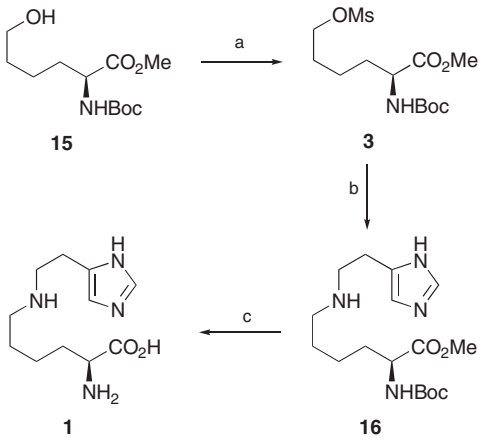
The next stage of the synthesis required the reduction of α,β-unsaturated aldehyde **9** to give 6-hydroxynorleucine derivative **15** (Scheme 3). Our initial strategy to carry out this transformation involved the catalytic hydrogenation of the alkene followed by the chemoselective reduction of aldehyde **10**. This approach was chosen as analogues of aldehyde intermediate **10** while known to be unstable have been isolated.[2c,9] However, hydrogenation of **9** at atmospheric pressure in the presence of 10% palladium on carbon gave only piperidine **12** in 44% yield.[10] We propose that compound **12** is formed by hydrogenation of **9** to give saturated aldehyde **10**. Cyclisation of **10** gives the enamine **11**, which is then further reduced under the hydrogenation conditions to give **12**. To prevent this cyclisation reaction, the proposed steps for the synthesis of **15** from **9** were reversed. Thus, sodium borohydride reduction of **9** gave the corresponding allylic alcohol **13** in 87% yield. Surprisingly, hydrogenation of **13** using 10% palladium on carbon at atmospheric pressure resulted in the reduction of the hydroxyl functional group as well as the alkene giving the norleucine derivative **14** in 44% yield. Similar results were obtained using 5% rhodium on carbon or palladium hydroxide as catalysts. While the hydrogena-



Scheme 3. Reagents and conditions: (a) H_2, 10% Pd/C, EtOH, 44%; (b) $NaBH_4$, MeOH, −40 °C, 87%; (c) H_2, 10% Pd/C, EtOAc, 44%; (d) H_2, PtO_2, EtOAc, 97%.

tion of allylic alcohols to the corresponding saturated alcohol is a common transformation,[11] examples of hydroxyl group reduction are also known.[12] Fortunately, the hydrogenation of allylic alcohol **13** with platinum oxide as the catalyst did give saturated alcohol **15**, after optimisation, in an excellent 97% yield.

The final stage of our synthesis of (*S*)-gizzerosine **1** required the coupling of histamine with an activated intermediate of 6-hydroxynorleucine derivative **15**. To this effect, **15** was converted to mesylate **3** under standard conditions (Scheme 4). Subsequent reaction with histamine in the presence of DBU gave coupled product **16** in 66% yield. Finally, acid mediated deprotection of **16** gave (*S*)-gizzerosine **1** in quantitative yield.[13]



Scheme 4. Reagents and conditions: (a) CH_3SO_2Cl, NEt_3, DMAP, CH_2Cl_2, 86%; (b) histamine, DBU, MeOH, Δ, 66%; (c) 6 M HCl, Δ, 100%.

In summary, we have developed a simple, practical approach for the synthesis of (*S*)-gizzerosine **1** in 10 steps and in 31% overall yield from L-aspartic acid **5**. This route utilised a Wittig reaction for the two-carbon homologation of L-aspartic acid semi-aldehyde **4** that was converted to 6-hydroxynorleucine derived mesylate **3** for efficient coupling with histamine **2**. While some problems were encountered in attempting the two-step conversion of α,β-unsaturated aldehyde **9** to 6-hydroxynorleucine derivative **15**, the optimised reactions involving sodium borohydride reduction of the aldehyde followed by platinum oxide catalysed hydrogenation of the alkene did allow this transformation to take place in excellent yield. Finally, this approach has been used specifically for the preparation of (*S*)-gizzerosine **1**. However, the substitution of histamine with other nucleophiles would lead to the late stage synthesis of a small library of gizzerosine derivatives for biological testing. Further work to achieve this goal is currently underway.

Acknowledgement

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13. Optical rotation for **1**: $[\alpha]_D^{23}$ +10.0 (*c* 0.2, H_2O); lit.[2c] $[\alpha]_D^{22}$ +10.3 (*c* 1.3, H_2O). Spectroscopic data were entirely consistent with those published for (*S*)-gizzerosine.[2c,4,5]