Facile Synthesis of (*S*)-Gizzerosine – A Potent Inducer of Gizzard Erosion in Chicks – Using Successive Zinc-Mediated and Palladium-Catalyzed Coupling Reactions

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This paper is dedicated to Professor Steven V. Ley, FRS, CBE, on the occasion of his 60th birthday.

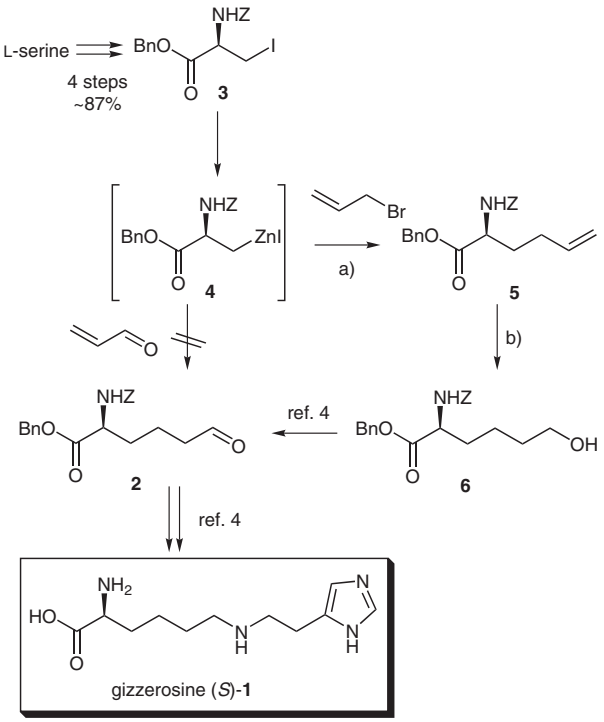
Abstract: Gizzerosine, a potent inducer of gizzard erosion in chicks, was synthesized using successive zinc-mediated and palladium-catalyzed coupling reactions as the key steps. The piperonyl moiety was used as a novel N-protecting group.

Key words: gizzerosine, gizzard erosion, chickens, total synthesis, histamine

'Black vomit' is a serious disease for chickens and is accompanied by gizzard erosion or ulceration.[1] In 1983, Naito et al. investigated the cause of this disease and isolated an amino acid gizzerosine (**1**), a potent inducer of gizzard erosion, which was generated during the heat treatment of brown fish meal.[2] The structure and absolute stereochemistry of **1** was confirmed by Mori's synthesis of racemic[3] and optically active forms.[4] Since **1** is in great demand as an important ulcerating agent for biologists, as well as a standard for the quality control of fish meal, we began to develop a practical synthesis of **1**. Here we describe a short and efficient synthesis of **1**.

At first, we targeted Mori's synthetic intermediate **2**,[4] which could be simply prepared by a zinc-mediated 1,4-addition reaction[5a] of the known iodide **3** with acrolein. However, this reaction did not proceed as expected and only the corresponding alanine derivative was formed. Next we tried to prepare Mori's other intermediate, alcohol **6**, using the coupling reaction with allyl bromide[5b] and hydroboration. Preparation of **5** was successful (98%) and hydroboration–oxidation gave the desired **6**, which could then be utilized in the formal synthesis of **1**. The yield for this step was improved from 32% to 68% by applying mildly alkaline conditions (NaOAc, H_2O_2, pH 7.5)[6] during the oxidation step to avoid concomitant hydrolysis of the benzyl group.

Next we aimed to improve the overall yield by changing the strategy. As shown in Scheme 2, chain elongation with 3-bromo-1-propenyl acetate **7**[7] afforded S_N2' product **9**, exclusively in 98% yield, instead of **8**. This allylic acetate **9** was a good substrate for palladium-catalyzed coupling reactions. Thus, reactions with histamine



Scheme 1 Formal synthesis of **1**. a) i. allyl bromide (1.2 equiv), Zn (6.0 equiv), $(CH_2Br)_2$ (0.3 equiv), TMSCl (0.06 equiv), DMF, 60 °C, 50 min ii. CuCN (1.0 equiv), LiCl (2.0 equiv), –78 °C, 2 h (98%); b) i. $BH_3{\cdot}SMe_2$ (0.5 equiv), THF, 0 °C, 12 h. ii. H_2O_2 (30%, 3.3 equiv), NaOAc (2.5 equiv) (68%).

derivatives were examined. Although histamine itself did not react, its derivatives **10a–d**[8] (Table 1) with electron-donating groups on the primary nitrogen atom were coupled with **9** to give **11a** (*N*-Bn), **11b** (*N*-PMB), **11c** [*N*-(3,4-dimethoxybenzyl)], or **11d** (*N*-piperonyl). Treatment of **11a** with Pd/C under hydrogen gave 7-*N*-benzylgizzerosine, however, deprotection of the *N*-benzyl group was unsuccessful even in an acidic suspension and palladium catalyst under 10 atm of hydrogen pressure. Deprotection of **11b** resulted in decomposition of the products. On the other hand, hydrogenation and deprotection of piperonyl derivative **11d** smoothly afforded gizzerosine (**1**) as the dihydrochloride salt using Pd/C in ethanol under a hydrogen atmosphere in 47% yield. As far as we know, this is the first case of using the piperonyl group as an N-protect-

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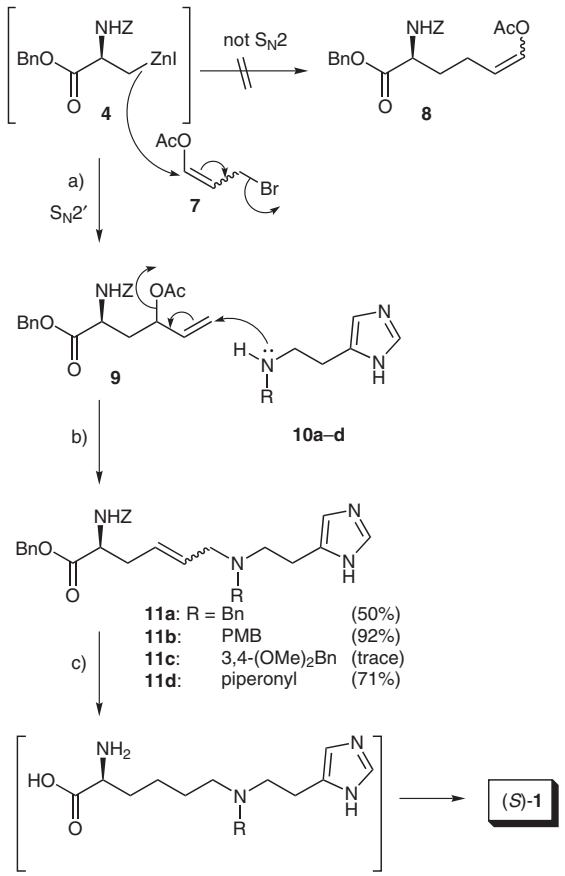
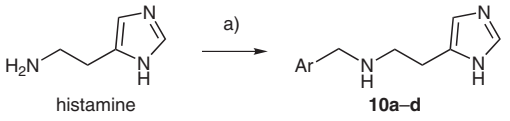


Scheme 2 Synthesis of **1** by a palladium-catalyzed coupling reaction. a) **7** (1.2 equiv), CuCN (1.0 equiv), LiCl (2.0 equiv), DMF, 2 h (98%); b) 2′-*N*-(*p*-R-$C_6H_4CH_2$)histamine (1.2 equiv), $Pd_2(dba)_3$ (0.05 equiv), PPh_3 (0.05 equiv), THF, 50 °C, 2 h; c) H_2, $Pd(OH)_2$/C, H_2O–THF–EtOH (1:1:3) (47% for **10d**).

Table 1 Preparation of 2′N-Protected Histamines



Entry	ArCHO	Products	Yields (%)
1	Benzaldehyde	**10a**	94
2	Anisaldehyde	**10b**	93
3	3,4-Dimethoxybenzaldehyde	**10c**	10
4	Piperonal	**10d**	89

[a] Conditions: ArCHO (2.5 equiv), $NaBH_4$ (2.0 equiv), MS 3Å, MeOH.

ing group. This low yield was due to the instability of **1** in the presence of palladium catalysts. The overall yield from **3** was 33% in three steps (29% from L-serine in seven steps). The spectroscopic data of **1** coincided with those reported.[3,4]

In summary, the short, efficient, and facile synthesis of gizzerosine (*S*)-**1**, a potent inducer of gizzard erosion, was achieved using successive zinc-mediated and palladium-catalyzed coupling reactions as the key steps. The piperonyl moiety was used as a novel N-protecting group.

NMR spectra were conducted at 300 MHz (^{1}H NMR) and 150 MHz (^{13}C NMR) with acetone as the reference (2.22 ppm, ^{1}H NMR; 215.94 ppm, ^{13}C NMR).

(+)-1·2HCl (9)

Amorphous solid; mp 250–251 °C (dec.) [Lit.[4] 251–252 °C (dec.)]; $[\alpha]_D^{22}$ +9.45 (*c* 0.555, H_2O) {Lit. $[\alpha]_D^{22}$ +10.3 (*c* 1.28, H_2O)}.

IR (ATR, Zn–Se): 3300–2300 (br s), 3116 (s), 2786 (s), 2450 (m), 1634 (s), 1601 (s), 1522 (s), 1462 (s), 1395 (s), 1348 (m), 1329 (m), 1235 (w), 1052 (w), 957 (w), 839 (w), 794 (w), 719 (w), 623 (m) cm^{-1}.

^{1}H NMR (D_2O): δ = 1.35–1.60 (2 H, m), 1.74 (2 H, quint, *J* = 7.5 Hz), 1.89 (2 H, m, pseudo q, *J* = 7.4 Hz), 3.11 (4 H, pseudo t, *J* = 6.6 Hz), 3.37 (2 H, pseudo t, *J* = 7.2 Hz), 3.75 (1 H, t, *J* = 6.0 Hz, CHC=O), 7.26 (1 H, br s), 8.30 (1 H, br s).

^{13}C NMR (D_2O): δ = 22.04, 22.91, 25.65, 30.38, 46.86, 47.72, 54.99, 116.93, 131.45, 135.69, 175.08 (C=O).

HRMS-FAB: *m/z* calcd for $C_{11}H_{21}N_4O_2$ $[M + H]^+$: 241.1665; found: 241.1671.

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