

# Total Synthesis of Dispyrin, Purpurealidin E, and Aplysamine-1

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**Bromotyrosine alkaloids dispyrin (1), purpurealidin E (2), and aplysamine-1 (3) isolated from marine sponge, were synthesized from commercially available tyramine (4) as a common starting material. The overall yield was 18%, 39%, and 22% for 1 from 4 in 5 steps, 2 in 5 steps, and 3 in 6 steps, respectively.**

**Key words** total synthesis; bromotyrosine alkaloid; marine sponge; dispyrin; purpurealidin E; aplysamine-1

Bromotyrosine alkaloids, well known as one of biologically active substances, possess a wide range of biological activities including anti Human immunodeficiency virus 1 (HIV-1) activity,<sup>1)</sup> anti methicillin-resistant *Staphylococcus aureus* (MRSA) activity,<sup>2)</sup> anti multidrug-resistant *Mycobacterium tuberculosis* activity,<sup>3)</sup> and anti-angiogenic activity.<sup>4)</sup> Because of these interesting activities, a number of synthetic studies on these alkaloids have been reported.<sup>5–11)</sup> Dispyrin (1)<sup>12)</sup> isolated from *Agelas dispar* (Agelasidae) and purpurealidin E (2)<sup>13)</sup> isolated from *Psammaphysilla purpurea* (Verongiidae) contain a structural motif similar to aplysamine-1 (3)<sup>14,15)</sup> isolated from *Pseudoceratina verroucosa* (Aplysinellidae), a brominated phenol having a 3-dimethylamino-1-propane (Fig. 1), known as the histamine H<sub>3</sub> receptor antagonist.<sup>16)</sup> But to the best of our knowledge, synthetic and biological studies on 1 and 2 have not been reported to date. In this paper we present first total synthesis of dispyrin (1) and purpurealidin E (2), and the chemical conversion of 2 to aplysamine-1 (3).

## Results

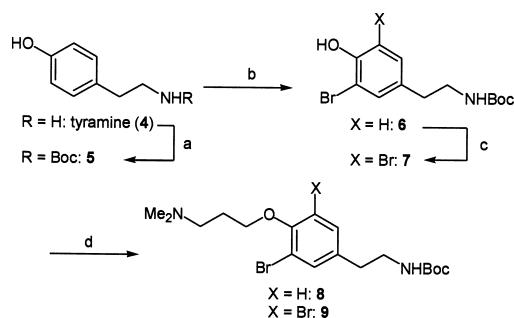
These alkaloids were synthesized from commercially available tyramine (4). Introduction of a bromine atom at 4 was carried out by treatment with tetrabutylammonium tribromide (TBAT)<sup>17)</sup> in the presence of calcium carbonate (CaCO<sub>3</sub>)<sup>18)</sup> after protection of the amino function as a Boc group<sup>19)</sup> to give a monobromophenol 6.<sup>20)</sup> A dibromophenol 7<sup>4)</sup> can be synthesized from 6 with the same condition. Mono- and di-brominated phenol 6 and 7 were treated with 3-dimethylamino-1-propanol in the presence of *p*-TsCl and benzyltriethylammonium chloride (BTAC) provided amino

ethers 8 and 9 in moderate yields (Chart 1).

After deprotection of *N*-Boc function in 8 followed by coupling with a bromopyrrole 11<sup>21)</sup> the expected dispyrin (1) was smoothly afforded, and good accordance of the <sup>1</sup>H- and <sup>13</sup>C-NMR data of dispyrin trifluoroacetate (1-TFA)<sup>22)</sup> with those of reported data<sup>12)</sup> were observed (Chart 2).

Deprotection of 7 with 10% HCl aq in MeOH to give purpurealidin E (2), followed by reductive *N*-methylation with NaBH(OAc)<sub>3</sub> and formalin into aplysamine-1 (3).<sup>23)</sup> Synthetic aplysamine-1 (3) and the hydrochloride salt of *N*-acetyl purpurealidin E (12-HCl)<sup>24)</sup> were spectroscopically identical with reported data<sup>13–15)</sup> (Chart 3).

In conclusion, we succeeded in the first total synthesis of dispyrin (1) and purpurealidin E (2), and the chemical conversion of 2 to aplysamine-1 (3), from commercially available tyramine as a common starting material. The overall yield was 18%, 39%, and 22% for 1 from 4 in 5 steps, 2 in 5



Reagent and conditions: (a) Boc<sub>2</sub>O, MeOH, rt, 2 h, 98%; (b) TBAT, CaCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>–MeOH (3 : 1), rt, 1 h, 77%; (c) TBAT, CaCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>–MeOH (3 : 1), rt, 1 h, 84%; (d) 3-dimethylamino-1-propanol, *p*-TsCl, BTAC, 20% NaOH aq, toluene, rt, 4 d, 45% on 6, 63% on 7.

Chart 1. Synthesis of Brominated Tyrosine Derivatives

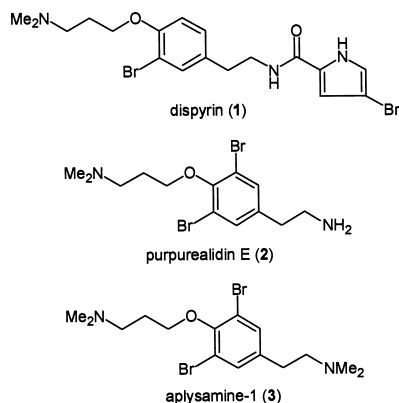
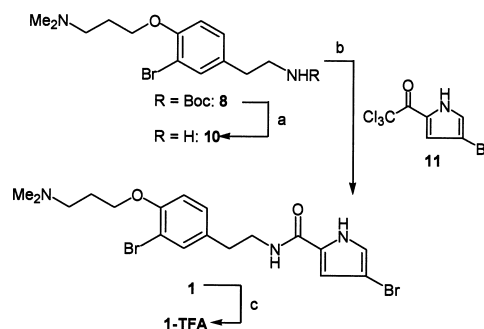


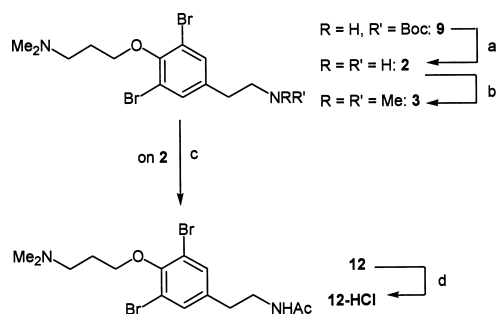
Fig. 1. Structure of Dispyrin (1), Purpurealidin E (2), and Aplysamine-1 (3)



Reagent and conditions: (a) 10% HCl aq, MeOH, rt, 1 h, quant.; (b) 11, pyridine, CHCl<sub>3</sub>, rt, 18 h, 54%; (c) CF<sub>3</sub>COOH, CH<sub>2</sub>Cl<sub>2</sub>–MeOH (3 : 1), rt, 1 h, quant.

Chart 2. Synthesis of Dispyrin (1)

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Reagent and conditions: (a) 10% HCl aq., MeOH, rt, 1 h, 98%; (b) 37% HCHO aq., NaBH(OAc)<sub>3</sub>, MeOH, rt, 3 h, 55%. (c) Ac<sub>2</sub>O, CHCl<sub>3</sub>, pyridine, rt, 18 h, 70%; (d) 10% HCl aq., MeOH, rt, 2 h, quant.

Chart 3. Synthesis of Purpurealidin E (**2**) and Aplysamine-1(**3**)

steps, and **3** in 6 steps, respectively.

## References and Notes

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- The selected data of **1-TFA**; IR (ATR):  $\nu$  3303, 1673  $\text{cm}^{-1}$ . <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  2.24 (2H, m), 2.79 (2H, t,  $J=7.3$  Hz), 2.95 (6H, s), 3.38 (2H, t,  $J=7.8$  Hz), 3.48 (2H, t,  $J=7.3$  Hz), 4.12 (2H, t,  $J=5.8$  Hz), 6.73 (1H, d,  $J=1.6$  Hz), 6.90 (1H, d,  $J=1.6$  Hz), 6.94 (1H, t,  $J=8.5$  Hz), 7.16 (1H, dd,  $J=8.5, 2.3$  Hz), 7.44 (1H, d,  $J=2.3$  Hz). <sup>13</sup>C-NMR (100 MHz, CD<sub>3</sub>OD):  $\delta$  25.5, 35.5, 41.8, 43.7, 57.0, 67.4, 97.4, 112.8, 113.2, 114.7, 122.7, 127.5, 130.2, 134.5, 135.1, 154.6, 162.5. ESI-MS:  $m/z$  472, 474, 476 [M+H]<sup>+</sup>.
- The selected data of synthetic **3**; IR (ATR): No characteristic absorption. <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  2.04 (2H, m), 2.29 (6H, s), 2.30 (6H, s), 2.53 (2H, t,  $J=8.1$  Hz), 2.65 (2H, t,  $J=7.8$  Hz), 2.73 (2H, t,  $J=8.1$  Hz), 4.02 (2H, t,  $J=6.2$  Hz), 7.46 (2H, s). <sup>13</sup>C-NMR (100 MHz, CD<sub>3</sub>OD):  $\delta$  29.0, 33.2, 45.3, 45.4, 57.5, 61.7, 72.6, 119.0, 134.1, 140.5, 152.8. ESI-MS:  $m/z$  407, 409, 411 [M+H]<sup>+</sup>, 429, 431, 433 [M+Na]<sup>+</sup>.
- The selected data of **12-HCl**; IR (ATR):  $\nu$  3319, 1678  $\text{cm}^{-1}$ . <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  1.94 (3H, s), 2.31 (2H, m), 2.76 (2H, t,  $J=7.2$  Hz), 2.97 (6H, s), 3.39 (2H, t,  $J=7.2$  Hz), 3.52 (2H, t,  $J=7.8$  Hz), 4.12 (2H, t,  $J=5.7$  Hz), 7.49 (2H, s). <sup>13</sup>C-NMR (100 MHz, CD<sub>3</sub>OD):  $\delta$  22.3, 26.4, 35.0, 41.6, 43.7, 57.1, 71.1, 118.8, 134.4, 140.4, 152.2, 173.6. ESI-MS:  $m/z$  421, 423, 425 [M+H]<sup>+</sup>, 443, 445, 447 [M+Na]<sup>+</sup>.