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

Makoto YOSHIDA and Kentaro YAMAGUCHI*

Faculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University; 1314–1 Shido, Sanuki, Kagawa 769–2193, Japan. Received June 23, 2008; accepted June 30, 2008; published online July 7, 2008

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,[1] anti methicillin-resistant *Staphylococcus aureus* (MRSA) activity,[2] anti multidrug-resistant *Mycobacterium tuberculosis* activity,[3] and anti-angiogenic activity.[4] Because of these interesting activities, a number of synthetic studies on these alkaloids have been reported.[5—11] Dispyrin (**1**)[12] isolated from *Agelas dispar* (Agelasidae) and purpurealidin E (**2**)[13] isolated from *Psammaplysilla purpurea* (Verongiidae) contain a structural motif similar to aplysamine-1 (**3**)[14,15] isolated from *Pseudoceratina verroucosa* (Aplysinellidae), a brominated phenol having a 3-dimethylamino-1-propane (Fig. 1), known as the histamine H_3 receptor antagonist.[16] 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**).

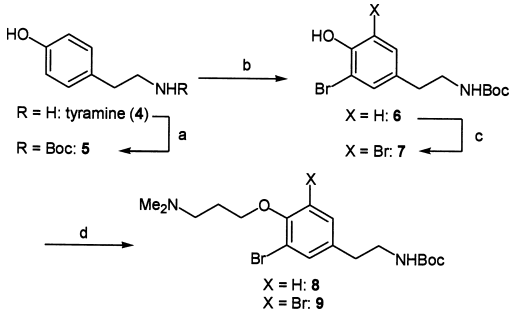
Results

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)[17] in the presence of calcium carbonate ($CaCO_3$)[18] after protection of the amino function as a Boc group[19] to give a monobromophenol **6**.[20] A dibromophenol **7**[4] 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**[21] the expected dispyrin (**1**) was smoothly afforded, and good accordance of the ^{1}H- and ^{13}C-NMR data of dispyrin trifluoroacetate (**1-TFA**)[22] with those of reported data[12] were observed (Chart 2).

Deprotection of **7** with 10% HCl aq in MeOH to give purpurealidin E (**2**), followed by reductive *N*-methylation with $NaBH(OAc)_3$ and formalin into aplysamine-1 (**3**).[23] Synthetic aplysamine-1 (**3**) and the hydrochloride salt of *N*-acetylpurpurealidin E (**12-HCl**)[24] were spectroscopically identical with reported data[13—15] (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_2O, MeOH, rt, 2 h, 98%; (b) TBAT, $CaCO_3$, CH_2Cl_2–MeOH (3 : 1), rt, 1 h, 77%; (c) TBAT, $CaCO_3$, CH_2Cl_2–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

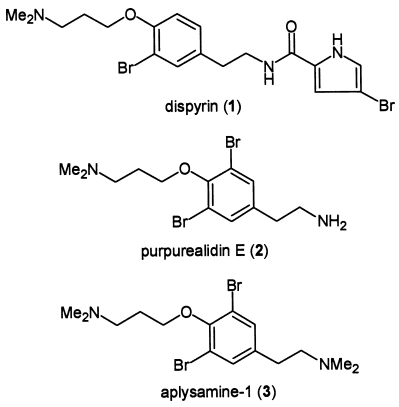
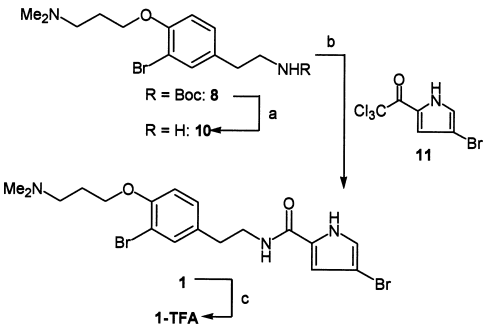


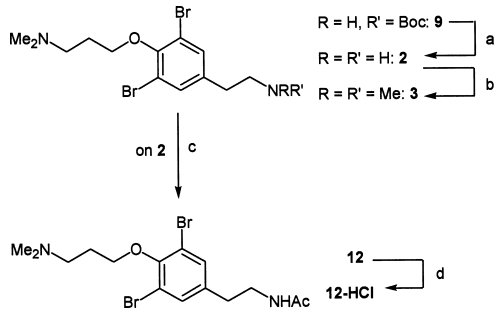
Fig. 1. Structure of Dispyrin (**1**), Purpurealidin E (**2**), and Aplysamine-1 (**3**)



Reagent and conditions: (a) 10% HCl aq, MeOH, rt, 1 h, quant.; (b) **11**, pyridine, $CHCl_3$, rt, 18 h, 54%; (c) CF_3COOH, CH_2Cl_2–MeOH (3 : 1), rt, 1 h, quant.

Chart 2. Synthesis of Dispyrin (**1**)

* To whom correspondence should be addressed. e-mail: yamaguchi@kph.bunri-u.ac.jp



Reagent and conditions: (a) 10% HCl aq., MeOH, rt, 1 h, 98%; (b) 37% HCHO aq., $NaBH(OAc)_3$, MeOH, rt, 3 h, 55%. (c) Ac_2O, $CHCl_3$, 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.

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22) The selected data of **1-TFA**; IR (ATR): ν 3303, 1673 cm^{-1}. ^{1}H-NMR (400 MHz, CD_3OD): δ 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). ^{13}C-NMR (100 MHz, CD_3OD): δ 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 $[M+H]^+$.
23) The selected data of synthetic **3**; IR (ATR): No characteristic absorption. ^{1}H-NMR (400 MHz, CD_3OD): δ 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). ^{13}C-NMR (100 MHz, CD_3OD): δ 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 $[M+H]^+$, 429, 431, 433 $[M+Na]^+$.
24) The selected data of **12-HCl**; IR (ATR): ν 3319, 1678 cm^{-1}. ^{1}H-NMR (400 MHz, CD_3OD): δ 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). ^{13}C-NMR (100 MHz, CD_3OD): δ 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 $[M+H]^+$, 443, 445, 447 $[M+Na]^+$.