Total Synthesis of the Marine Bromotyrosine Alkaloid Moloka'iakitamide

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The first total synthesis of moloka'iakitamide (1), a recently reported bromotyrosine alkaloid from *Pseudoceratina arabica* with oxalamide moiety, was achieved in 7 steps from commercially available tyramine (26% overall).

Key words total synthesis; bromotyrosine alkaloid; marine sponge; moloka'iakitamide; tyramine; 2-chloro-1,3-dimethylimidazolinium chloride

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] These are also known as therapeutically important G protein-coupled receptors, the histamine H_2 and H_3 receptors[5,6] and the adrenergic α_{1D} and α_{2A} receptors[6] antagonist. Because of these interesting activities, a number of synthetic studies on these alkaloids have been reported.[6—16] Moloka'iakitamide (**1**)[17] has been isolated from the Red Sea sponge *Pseudoceratina arabica* (Pseudoceratinidae) and shows significant parasympatholytic effects on isolated rabbit heart and jejunum, and weakly antifungal activity, contains one bromotyrosine unit and oxalamide moiety (Fig. 1). In this paper we present the first total synthesis of moloka'iakitamide (**1**).

Results

As outlined in Chart 1, retrosynthetic analysis of moloka'iakitamide (**1**) envisaged an alkylation of brominated tyramine (**2**) with protected amine derivative (**3**), followed by an amide coupling between oxamic acid (**4**).

Our synthesis began with commercially available tyramine (**5**). Introduction of a bromine atom at **5** was carried out by reported method in 2 steps.[15] Di-brominated phenol (**6**) was treated with iodide (**8**), which was prepared from *N*-(3-hydroxyproyl)phthalimide (**7**),[18] in the presence of potassium carbonate (K_2CO_3) and benzyltriethylammonium chloride (BTAC) provided ether (**9**) in high yields (Chart 2).

After dephthalimidation of **9** with hydrazine monohydrate in ethanol to give amine (**10**), followed by coupling with oxamic acid (**4**) using 2-chloro-1,3-dimethylimidazolinium chloride (DMC) as a dehydrating agent,[19] the *N*-Boc-moloka'iakitamide (**11**) was afforded in moderate yield. Deprotection of *N*-Boc function in **11** with acidic condition, and the residue was made alkaline to give moloka'iakitamide (**1**) (Chart 3). Thus, the first total synthesis of moloka'iakitamide (**1**) was completed.

The ^{1}H- and ^{13}C-NMR data of our synthetic moloka'iakitamide (**1**) were not in complete accordance with those re-

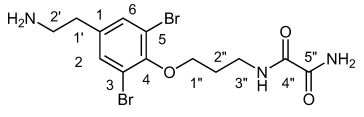


Fig. 1. Structure of Moloka'iakitamide (**1**), a Bromotyrosine Alkaloid from *Pseudoceratina arabica*

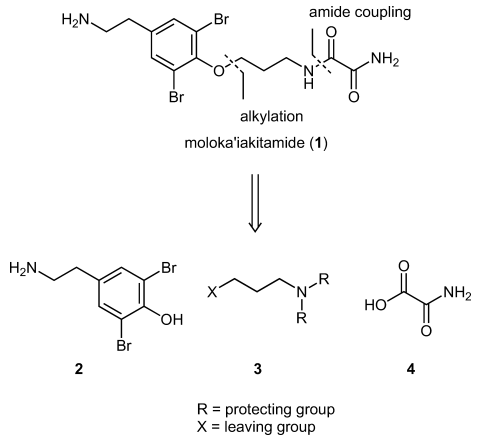
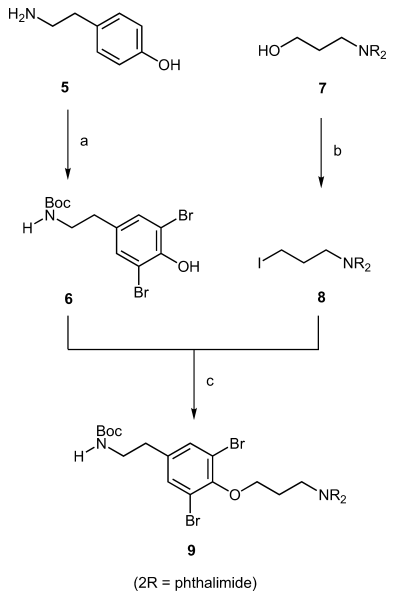


Chart 1. Retrosynthetic Analysis of Moloka'iakitamide (**1**)



Reagent and conditions: (a) see ref. 15, 63% in 2 steps; (b) see ref. 18, 78%; (c) K_2CO_3, BTAC, CH_3CN, rt, 48 h, quant.

Chart 2. Synthesis of Moloka'iakitamide (**1**) Part 1: Alkylation of Tyramine Derivative

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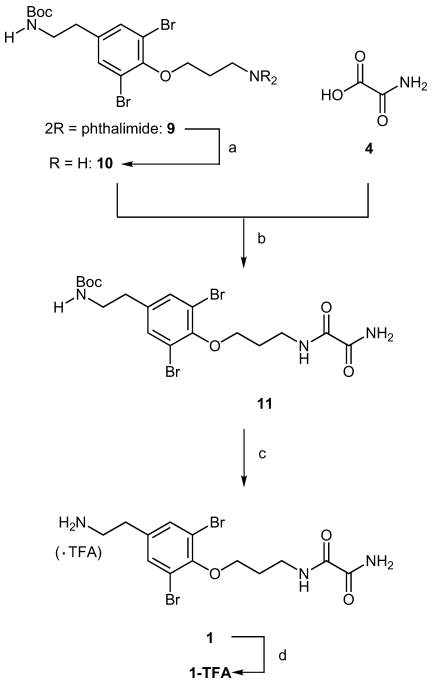
ported for natural moloka'iakitamide (**1**) by Badr *et al.*[17] On the other hand, moloka'iakitamide trifluoroacetate (**1-TFA**), which was prepared from **1** and trifluoroacetic acid, were spectroscopically identical with reported data (Table 1). Thus, the original report of natural moloka'iakitamide (**1**) by Badr *et al.*,[17] characterized a protonated salt form, such as **1-TFA**, and not the free-base **1**.

In conclusion, we succeeded in the first total synthesis of moloka'iakitamide (**1**) from commercially available tyramine as a starting material. The overall yield was 26% for moloka'iakitamide (**1**) from tyramine (**5**) in 7 steps.

Experimental

All manipulations were carried out under air atmosphere. IR spectra were recorded on a JASCO FT/IR-6300 spectrophotometer; ATR=attenuated total reflectance system. NMR spectra were recorded on a JEOL JNM-ECX400 (400 MHz for ^{1}H and 100 MHz for ^{13}C). Using tetramethylsilane (0.00 ppm) in $CDCl_3$ or residual methanol (CH_3OH) (3.31 ppm) in CD_3OD as internal standard for ^{1}H-NMR. Using the middle resonance of $CDCl_3$ (77.0 ppm) or CD_3OD (49.0 ppm) as an internal standard for ^{13}C-NMR. ESI-MS were recorded on a JEOL JMS-T100LC mass spectrometer. There used for TLC Silica gel 60 F_{254} plates (Merck No. 5715) and for column chromatography spherical Silica gel 60, particle size 63—210 mm (Kanto Chemical No. 37564-85 for normal, No. 37565-84 for neutral). All reagents and solvents are available from commercial sources and were used as received. 2-Chloro-1,3-dimethylimidazolinium chloride (DMC) was purchased from Tokyo Kasei Co. Inc. Compound **6** and **8** were prepared according to the literature procedure.[15,18]



Reagent and conditions: (a) $H_2NNH_2\cdot H_2O$, EtOH, rt, 24 h, 93%; (b) DMC, Et_3N, DMF, rt, 2 h, 61%; (c) CF_3COOH, CH_2Cl_2, rt, 18 h, then NaOH aq., 72%; (d) CF_3COOH, CH_2Cl_2, rt, 1 h, quant.

Chart 3. Synthesis of Moloka'iakitamide (**1**) Part 2: Formation of Oxalamide Moiety

Synthesis of Ether (9) A mixture of phenol (**6**) (410 mg, 1.04 mmol), iodide (**8**) (325 mg, 1.03 mmol), BTAC (24 mg, 0.105 mmol), and K_2CO_3 (290 mg, 2.10 mmol) in CH_3CN (6.0 ml) was stirred at rt for 48 h. The reaction mixture was poured into water, and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by SiO_2-column chromatography (eluent: toluene/AcOEt=22 : 1) to give **9** as a colorless amorphous (602 mg, quant.). IR (ATR) ν: 3332, 1775, 1706, 1673 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (9H, s), 2.27 (2H, m), 2.71 (2H, t, J=6.7 Hz), 3.31 (2H, dt, J=6.7, 6.6 Hz), 3.99 (2H, t, J=7.3 Hz), 4.08 (2H, t, J=6.2 Hz), 4.58 (1H, br), 7.31 (2H, s), 7.71 (2H, m), 7.86 (2H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.4 (CH_3), 29.1 (CH_2), 34.9 (CH_2), 35.5 (CH_2), 41.4 (CH_2), 70.9 (CH_2), 79.5 (C), 118.2 (C), 123.2 (CH), 132.1 (C), 132.9 (CH), 133.9 (CH), 137.8 (C), 151.7 (C), 155.7 (C), 168.3 (C). ESI-MS m/z: 603 $[C_{24}H_{26}Br_2^{79}N_2O_5+Na]^+$, 605 $[C_{24}H_{26}Br^{79}Br^{81}N_2O_5+Na]^+$, 607 $[C_{24}H_{26}Br_2^{81}N_2O_5+Na]^+$. HR-ESI-MS m/z: 605.00907 (Calcd for $[C_{24}H_{26}Br^{79}Br^{81}N_2O_5+Na]^+$, 605.00857).

Synthesis of Amine (10) To a solution of ether (**9**) (140 mg, 0.24 mmol) in EtOH (1.5 ml) hydrazine monohydrate (0.40 g) was added, and the mixture was stirred at rt for 24 h. The reaction mixture was diluted with AcOEt, washed with water and brine, dried over K_2CO_3, and evaporated to yield **10** as a pale brown oil (101 mg, 93%). This material was used without further purification. IR (ATR) ν: 3365, 1697 cm^{-1}. ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.40 (9H, s), 1.99 (2H, m), 2.69 (2H, t, J=6.9 Hz), 2.95 (2H, t, J=6.9 Hz), 3.22 (2H, t, J=6.9 Hz), 4.03 (2H, t, J=6.0 Hz), 7.42 (2H, s). ^{13}C-NMR (100 MHz, CD_3OD) δ: 28.8 (CH_3), 33.8 (CH_2), 35.8 (CH_2), 39.9 (CH_2), 42.4 (CH_2), 72.5 (CH_2), 80.0 (C), 118.8 (C), 134.6 (CH), 140.0 (C), 152.7 (C), 158.3 (C). ESI-MS m/z: 451 $[C_{16}H_{24}Br_2^{79}N_2O_3+H]^+$, 453 $[C_{16}H_{24}Br^{79}Br^{81}N_2O_3+H]^+$, 455 $[C_{16}H_{24}Br_2^{81}N_2O_3+H]^+$. HR-ESI-MS m/z: 451.02582 (Calcd for $[C_{16}H_{24}Br_2^{79}N_2O_3+H]^+$, 451.02319).

Synthesis of *N*-Boc-moloka'iakitamide (11) To a solution of amine (**10**) (80 mg, 0.18 mmol), oxamic acid (**4**) (18 mg, 0.20 mmol), and Et_3N (0.10 ml, 0.72 mmol) in *N*,*N*-dimethylformamide (DMF) (1.5 ml) 2-chloro-1,3-dimethylimidazolinium chloride (DMC, 34 mg, 0.20 mmol) was added, and the mixture was stirred at rt for 2 h. The reaction mixture was poured into water, and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by SiO_2-column chromatography (eluent: $CHCl_3$/AcOEt=7 : 2) to give **11** as a colorless amorphous (56 mg, 61%). IR (ATR) ν: 3381, 3356, 3311, 3222, 1681, 1652 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (9H, s), 2.11 (2H, m), 2.72 (2H, t, J=6.9 Hz), 3.33 (2H, dt, J=6.7, 6.4 Hz), 3.68 (2H, dt, J=6.5, 6.4 Hz), 4.07 (2H, t, J=6.8 Hz), 4.57 (1H, br), 5.59 (1H, br), 7.32 (1H, br), 7.34 (2H, s), 7.85 (1H, br). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.3

Table 1. ^{1}H- and ^{13}C-NMR Spectroscopic Data for Moloka'iakitamide (**1**)[a]

Position	Synthetic **1**		**1-TFA**		Natural **1**[b]	
	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1		139.2		136.8		137.5
2, 6	7.43 s	132.9	7.57 s	132.9	7.57 s	132.9
3, 5		117.7		118.0		118.1
4		151.3		152.0		152.1
1′	2.67 t (7.1)	36.8	2.95 t (7.4)	31.7	2.93 t (7.5)	31.7
2′	2.82 t (7.1)	42.6	3.21 t (7.4)	39.9	3.19 t (7.5)	40.0
1″	4.02 t (6.0)	70.8	4.09 t (6.0)	70.7	4.10 t (6.5)	70.7
2″	2.08 m	29.1	2.15 m	28.9	2.14 quin. (6.5)	28.9
3″	3.55 t (6.9)	37.4	3.61 t (6.8)	36.6	3.60 t (6.5)	36.5
4″		160.5		160.4		160.4
5″		162.7		162.5		162.5

a) The NMR data were obtained at 400/100 MHz for ^{1}H/^{13}C. *b*) Reported by Badr *et al.*[17]

(CH_3), 29.1 (CH_2), 34.8 (CH_2), 37.1 (CH_2), 41.4 (CH_2), 70.5 (CH_2), 79.5 (C), 118.0 (C), 132.9 (CH), 138.0 (C), 151.2 (C), 155.9 (C), 159.5 (C), 161.9 (C). ESI-MS *m/z*: 544 $[C_{18}H_{25}Br_2^{79}N_3O_5+Na]^+$, 546 $[C_{18}H_{25}Br^{79}Br^{81}N_3O_5+Na]^+$, 548 $[C_{18}H_{25}Br_2^{81}N_3O_5+Na]^+$. HR-ESI-MS *m/z*: 546.00479 (Calcd for $[C_{18}H_{25}Br^{79}Br^{81}N_3O_5+Na]^+$, 546.00382).

Synthesis of Moloka'iakitamide (1) To a solution of *N*-Boc-moloka'iakitamide (**11**) (56 mg, 0.11 mmol) in CH_2Cl_2 (1.0 ml) trifluoroacetic acid (0.1 ml) was added, and the mixture was stirred at rt for 18 h. The reaction mixture was poured into water, and washed with Et_2O. The aqueous layer was alkalized with 20% NaOH aq. and extracted with $CHCl_3$. The organic layer was washed with water and brine, dried over K_2CO_3, and evaporated to afford **1** as a colorless amorphous (32 mg, 72%). IR (ATR) ν: 3367, 3341, 3301, 1641 cm^{-1}. ^{1}H-NMR (400 MHz, CD_3OD) δ: 2.08 (2H, m), 2.67 (2H, t, J=7.1 Hz), 2.82 (2H, t, J=7.1 Hz), 3.55 (2H, t, J=6.9 Hz), 4.02 (2H, t, J=6.0 Hz), 7.43 (2H, s). ^{13}C-NMR (100 MHz, CD_3OD) δ: 29.1 (CH_2), 36.8 (CH_2), 37.4 (CH_2), 42.6 (CH_2), 70.8 (CH_2), 117.7 (C), 132.9 (CH), 139.2 (C), 151.3 (C), 160.5 (C), 162.7 (C). ESI-MS *m/z*: 422 $[C_{13}H_{17}Br_2^{79}N_3O_3+H]^+$, 424 $[C_{13}H_{17}Br^{79}Br^{81}N_3O_3+H]^+$, 426 $[C_{13}H_{17}Br_2^{81}N_3O_3+H]^+$. HR-ESI-MS *m/z*: 423.96916 (Calcd for $[C_{13}H_{17}Br^{79}Br^{81}N_3O_3+H]^+$, 423.96945).

Synthesis of Moloka'iakitamide Trifluoroacetate (1-TFA) To a solution of moloka'iakitamide (**1**) (30 mg, 0.071 mmol) in CH_2Cl_2 (1.0 ml) trifluoroacetic acid (0.1 ml) was added, and the mixture was stirred at rt for 1 h. The reaction mixture was evaporated to yield **1-TFA** as a colorless amorphous (39 mg, quant.). IR (ATR) ν: 3392, 3276, 1682, 1652 cm^{-1}. ^{1}H-NMR (400 MHz, CD_3OD) δ: 2.15 (2H, m), 2.95 (2H, t, J=7.4 Hz), 3.21 (2H, t, J=7.4 Hz), 3.61 (2H, t, J=6.8 Hz), 4.09 (2H, t, J=6.0 Hz), 7.57 (2H, s). ^{13}C-NMR (100 MHz, CD_3OD) δ: 28.9 (CH_2), 31.7 (CH_2), 36.6 (CH_2), 39.9 (CH_2), 70.7 (CH_2), 118.0 (C), 132.9 (CH), 135.8 (C), 152.0 (C), 160.4 (C), 162.5 (C). ESI-MS *m/z*: 422 $[C_{13}H_{17}Br_2^{79}N_3O_3+H]^+$, 424 $[C_{13}H_{17}Br^{79}Br^{81}N_3O_3+H]^+$, 426 $[C_{13}H_{17}Br_2^{81}N_3O_3+H]^+$, 444 $[C_{13}H_{17}Br_2^{79}N_3O_3+Na]^+$, 446 $[C_{13}H_{17}Br^{79}Br^{81}N_3O_3+Na]^+$, 448 $[C_{13}H_{17}Br_2^{81}N_3O_3+Na]^+$. HR-ESI-MS *m/z*: 445.95558 (Calcd for $[C_{13}H_{17}Br^{79}Br^{81}N_3O_3+Na]^+$, 445.95139).

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